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The impact of organised screening programmes on the stage-specific incidence of breast cancer in some Italian areas

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Abstract

The aim of this study was to examine the effects of mammographic screening programmes on stage-specific incidence of breast cancer. The study compared prescreening and screening periods in seven areas in Italy, primarily evaluating the first screening round. All 17 617 breast cancers (16 554 invasive, 1063 *in situ*) registered in women aged 40–79 years between 1988 and 1999 were analysed through age-standardised rates and Poisson regression models. For all areas, independent of the baseline rates, the introduction of screening increased incidence for invasive cancers overall and, more markedly, for early cancers (screening/prescreening ratio: range 1.07–1.47 and 1.23–1.82, respectively), modifying the pattern of age-specific rates. The multiple regression analysis showed that the percentage of cases diagnosed at screening explained most of the increase; a residual effect of diagnosis period (screening versus prescreening) suggested a role for 'spontaneous' early detection in ages outside of the screening programme. Advanced cases did not show consistent variations across the registries for those aged 40–79 years (range: 0.91–1.21), whereas a more coherent picture was observed for those aged 50–69 years. In one area, a moderate reduction in the number of 'advanced' cases in the second screening period was observed. For all stages, the age-specific incidence rates of cases diagnosed outside of the screening programme for the age groups 50–69 years were lower than the corresponding rates in the prescreening period, suggesting a shift from the usual clinical services to the screening programme. Our results confirmed the increase in early-stage cancers occurring at the start of screening, and substantially explained the rise in breast cancer incidence. In addition, our study confirms the importance of cancer registries in monitoring the effect of breast cancer screening and the validity, for this purpose, of the linkage between cancer registries and screening programme databases.

Keywords: Breast cancer; Stage; Mammographic screening; Incidence; Cancer registry

1. Introduction

Some randomised trials have shown that mammographic screening reduces breast cancer mortality in women aged 50–69 years, with an average reduction of approximately 25–30%, providing the scientific basis for this screening [1,2]. However, a recent meta-analysis concluded that there is no reliable evidence that screening for breast cancer reduces all-cause mortality [3]. This resulted in a wide debate on the efficacy of breast cancer screening programmes, on the methods used in the meta-analysis and on the interpretation of results [4–7]. An updated overview of the Swedish randomised controlled trials confirmed the benefit of screening in terms of breast cancer mortality, persisting after a long-term follow-up [4].

The effect on breast cancer mortality has been considered the basic measure to evaluate screening efficacy [8]. However, this reduction is expected to occur 6–7 years or more after the start of screening [8,9]. Therefore, the reduction of advanced breast cancer rates in a population in which a long-term screening programme is ongoing

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has been proposed as an early indicator of efficacy. This measure is particularly appropriate in public health screening programmes, outside of randomised trials [8].

A reduction in stage-specific incidence at the population level can only be documented where a cancer registry provides a non-biased estimate of breast cancer incidence rates by stage over time. In recent years, screening has been introduced in several European countries as a public health programme at the population level [10–13]. The need for a well-designed surveillance of the impact on the population of ongoing breast cancer screening is therefore of paramount importance given the recent debate.

Since 1996, the Italian Ministry of Health has promoted local mammographic screening initiatives based upon the use of a nationally agreed protocol. The presence in the screening area of a population-based breast cancer registry, aimed at checking early efficacy indicators of the screening programme, is one of the conditions recommended in the protocol. In the late 1990s, some Regional governments began population-based mammographic screening programmes for women aged 50–69 years, mainly in areas where a population-based cancer registry was already operating.

This paper describes the effect of breast cancer screening programmes on the stage-specific incidence of breast cancer, comparing prescreening and screening periods in seven areas in Italy where screening is ongoing and population cancer registries are active.

2. Patients and methods

2.1. Population under study and source of cases

The study included 17 617 breast cancers (ICD-9 174 and 233.0) diagnosed among women aged 40–79 years, who were resident in seven areas (mainly located in Central-Northern Italy) where a population-based cancer registry was active and mammographic screening was ongoing. Each registry contributed at least 400 cases (Table 1). Death Certificate Only (DCO) cases ($n = 93$, less than 1%) were excluded from the analysis. The population size included in the study was stable before and after the beginning of screening in all registries, excepting Romagna, where the population covered by cancer registration substantially increased in the screening period. The year of screening activation differed by area, being earlier in Florence and Turin and being implemented more recently in Ferrara and Parma, where screening began in 1997–1998. The prescreening/screening periods were categorised on the basis of the starting year, or, when the programme did not start at the beginning of the year, on the basis of the starting month.

For each case, the following variables were collected: place of residence, age (5-year age groups), size of the tumour in mm, pT, pN, number of examined and positive lymph nodes, presence of metastasis, histological type and surgical treatment.

Invasive cases were considered as 'early' stage when belonging to the categories pT1, pN0, M0 and pT1, pNx, M0 (the latter group was 8–9% of 'early' cases). Otherwise, invasive cases were classified as 'advanced' (size was >20 mm or N+ or M+), or 'unknown' stage (clinical or pathological), when defined as Tx/pTx/, Nx/pNx and Mx. In addition, independent of the nodal status, the cancer size categories $\leqslant 10$ (pT1a and pT1b) and 11–20 mm (pT1c) were analysed.

2.2. Statistical analysis

Age-adjusted incidence rates (age: 40–79 years; standard: European population) were calculated by registry

Table 1
Italian registries participating in the study: period of incidence, women resident in the area (mean number/year) and all incident (DCO excluded), *in situ* and invasive cases by screening period, age 40–79 years

Cancer registry	Study period		Women resident by period ($N \times 1000$)		Incident cases by period (N)						
	Prescreening	Screening			Prescreening			Screening			
			Prescreening	Screening	All cases	*In situ* cases	Invasive cases	All cases	*In situ* cases	Invasive cases	Screen-detected cases, age 50–69 years (%)
Ferrara	1992–1997 (Oct.)	1997 (Nov.)–1999	98	100	1395	67	1328	703	33	670	52.2
Florence city	1989–1990 (Sept.)	1990 (Oct.)–1996	114	114	495	23	472	1916	108	1808	43.3
Modena	1992–1995 (Sept.)	1995 (Oct.)–1998	151	155	1391	93	1298	1455	173	1282	27.7[a]
Parma	1994 and 1997[c]	1998	102	103	518	24	494	296	26	270	39.3
Ragusa	1993–1994	1995–1997	62	64	157	0	157	288	2	286	12.0[a]
Romagna	1989–1994[c]	1997–1999	158	248	2033	84	1949	2404	216	2188	48.1
Turin city	1988–1991	1992–1995	258	249	2073	68	2005	2493	146	2347	13.8[b]
Total	1988–1997	1990–1999	943	1033	8062	359	7703	9555	704	8851	–

DCO, Death Certification Only.

[a] During the study period, the programme was limited to some municipalities of the area covered by the cancer registration.

[b] During the study period, the programme mainly invited women aged 50–59 years.

[c] The incidence data stratified by TNM were not available in the years 1995–1996 for Parma and in Romagna.

and by period of incidence. Multiple Poisson regression models were fitted to assess the effect on incidence of the age-registry specific percentage of cases diagnosed at screening and of the period of diagnosis (screening versus prescreening), adjusted for age groups and for registry. The percentage of cases diagnosed at screening represents a proxy variable indicating the overall diffusion of the programme in the area, dependent both on the proportion of women invited at a given time and their compliance. The Poisson model provides estimates of the risk of cancer in a given category of a covariate in comparison with the reference category (incidence rate ratio (IRR)). The check of a fitted model against the data was performed through the 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). For each IRR, the 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

In the screening period, the percentage of cases diagnosed at screening among women aged 50–69 years ranged between 52.2% and 12.0%, due to variability in the diffusion of the programme (Table 1). In fact in Modena and Ragusa, the screening was limited to some municipalities of the registry areas, whereas in Turin (during the study period) the invitation mainly involved women in the age group 50–59 years. Of the whole series, 16 554 cases were invasive cancer and 1063 *in situ* cancers. Ductal carcinoma *in situ* (DCIS) increased from approximately 3.5% in the prescreening period to 6.5% after the start of screening programmes.

Among the invasive cases included in the analysis, 94% underwent surgery. Among these, the completeness was 94% for pT or size in mm, 91% for pN and 85% for the number of examined lymph nodes. In approximately 6%, the stage was classified as 'unknown'. In Ragusa, the percentage of unknown stages was very high, because of the high proportion of cases resected in surgical departments outside of the area covered by the registry. The number of lymph nodes examined was quite homogeneous (prescreening period: mean = 16.1, standard deviation (S.D.) = 6.9, range = 13.9–18.9; screening period: mean = 17.6, S.D. = 7.0, range = 15.9–19.1).

All invasive and stage-specific prescreening incidence rates (age-adjusted on the European population), and screening–prescreening rate ratio stratified by registry are presented in Table 2 (age 40–79 years). The years analysed in the prescreening and screening periods are reported in Table 1, except for some registries, for which a long period of incidence were available. For these registries, only the 3-year periods, when available, before and/or after the beginning of screening were compared (see Table 2 footnote). In the prescreening period, age-adjusted incidence rates of all invasive cases, similar in

Table 2
Prescreening incidence rates (age-adjusted, standard: European population, ×100 000) and screening/prescreening incidence rate ratio by cancer registry[a]. All invasive stages, early and advanced breast cancer. Age 40–79 years

Registry	Cancer stage					
	Invasive overall		Early		Advanced	
	Prescreening period incidence rate and 95% CI	Screening/ prescreening incidence rate ratio	Prescreening incidence rate and 95% CI	Screening/ prescreening incidence rate ratio	Prescreening incidence rate and 95% CI	Screening/ prescreening incidence rate ratio
Ferrara	217.4 (199.7–235.2)	1.34 $P<0.001$	93.8 (82.0–105.5)	1.59 $P<0.001$	108.4 (96.0–120.9)	1.21 $P=0.02$
Florence	231.2 (209.3–253.1)	1.09 $P=0.24$	95.0 (80.8–109.2)	1.23 $P=0.02$	116.7 (101.2–132.2)	1.00 $P=0.95$
Modena	216.1 (204.0–228.3)	1.11 $P=0.006$	94.4 (86.3–102.6)	1.39 $P<0.001$	121.2 (112.1–130.2)	0.91 $P=0.07$
Parma	226.0 (204.9–247.1)	1.07 $P=0.24$	81.7 (68.9–94.5)	1.47 $P<0.001$	129.1 (113.3–144.9)	0.95 $P=0.6$
Ragusa	121.4 (102.0–140.7)	1.18 $P=0.01$	n.c.	– –	n.c.	– –
Romagna	195.1 (183.8–206.4)	1.42 $P<0.001$	78.4 (71.2–85.6)	1.82 $P<0.001$	108.7 (100.2–117.1)	1.10 $P=0.054$
Turin	185.4 (177.1–193.7)	1.20 $P<0.001$	57.8 (53.1–62.4)	1.48 $P<0.001$	109.5 (103.1–115.9)	1.12 $P=0.006$

n.c., not calculated.

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

most registries, were lower in Romagna and in Turin and, particularly, in Ragusa, the only Southern Italian area included in the study. Early cases showed a wider variation than the advanced ones, the higher/lower rate ratios being 1.64 and 1.19, respectively. For two registries (the neighbouring areas of Ferrara and Romagna) with a longer incidence period before the beginning of the screening, we subdivided the whole interval into two 3-year periods. The age-adjusted incidence rates were substantially similar across the two periods for all stages (Romagna, 1989–1991: 195.7/100 000, 95% CI: 180.9–210.5; Ferrara, 1992–1994: 229.9/100 000, 95% CI: 205.4–240.4), and for early and advanced cases (data not shown).

Incidence rates in the screening period were higher than in the prescreening period for all invasive and, particularly, for early cancers. Indeed the screening/prescreening incidence rate ratio ranged between 1.07 and 1.42 for all stages and between 1.23 and 1.82 for early cancers. In all registries, the difference was higher among women aged 50-69 years (data not shown). Before the beginning of the screening programmes, the highest incidence of all stages and of early cancers was observed in Florence. This registry experienced the lowest increase of the respective incidence rates after the start of screening. For the whole age group included in the study (40–79 years), the variation in incidence according to screening was not consistent for advanced cases. Indeed, in the screening period, incidence rates were higher in some registries, whereas other registries reported similar or lower incidence rates. When the comparison was restricted to those aged 50–69 years, the incidence rate ratio was approximately 1.0 for Florence and Modena, whereas it ranged from between 1.10 and 1.44 for the other areas. In one registry (Florence), results for the second 3-year screening period are suggestive of a decreasing trend in the incidence rates for all stages, early and advanced cancers, even if the differences were not significant (1994–1996 age-adjusted incidence rates, respectively: 229.3/100 000, 95% CI: 212.7–246.0; 106.8/100 000, 95% CI: 95.4–118.2; 113.4/100 000, 95% CI: 101.6–125.4). A concomitant significant reduction of cases with unknown stage was observed in the second 3-year screening period (1994–1996 incidence rate: 9.1/100 000, 95% CI:6.0–12.3, versus 19.5/100 000, 95% CI: 13.3–25.6, in the prescreening period).

Several pooled models have been fitted comparing the periods before and after the beginning of screening (as defined in Table 2). For all invasive stages, the multivariate model including Ferrara, Florence, Parma and Modena and the variables registry, age groups and percentage of screen-detected cases showed an acceptable fit (model deviance: $P=0.09$), whereas the models showed an insufficient fit when the other registries were included. The introduction in the above specified model of the period of diagnosis (screening versus prescreening) did not show a significant effect (LRS: $P=0.66$). For early cancers, the multivariate model showed an appropriate fit when the same group of four registries was analysed and the variables registry, age groups, percentage of screen-detected cases and period of diagnosis were included (model deviance: $P=0.46$). Therefore, the percentage of screen-detected cases had a significant positive effect on the increase in incidence both for all invasive stages and for early cancers (the increase being, approximately 6 and 9% for every 10% increase in screen-detected cases, $P<0.001$). After adjustment for this variable too, the incidence of early cancer in the screening period remained 14% higher ($P=0.019$) than in the prescreening period. Introducing the number of examined lymph nodes and the incidence rates of cases with unknown stage as a proxy of the precision of stage definition did not change the effects on the early case incidence rates (data not shown).

For all invasive stages (pool of Ferrara, Florence, Modena and Parma registries), the difference in the rates between the prescreening and screening periods mostly concerned the age groups involved in the screening, with a peak among women aged 65–69 years (Fig. 1). Early cases followed a similar, but more marked pattern (Fig. 2). During the screening period, the age-specific incidence rates of cancers of all stages and early cancers diagnosed outside of the screening programme were lower than the corresponding rates in the prescreening period.

The analysis of pT1 cases by cancer size (Table 3) showed that the increase of incidence rates in the screening period concerned both $\leqslant 10$ and 11–20 mm cancers. For most registries, the increase was more evident for the smaller cancers.

4. Discussion

The effect of mammographic screening on invasive breast cancer stage-specific incidence rates is shown in

Table 3
Screening/prescreening incidence rate ratio[a] by cancer registry; invasive breast cancer, size $\leqslant 10$ mm and 11–20 mm, age 40–79 years

Registry	Cancer size			
	$\leqslant 10$ mm		11–20 mm	
Ferrara	1.21	$P=0.001$	1.27	$P<0.001$
Florence	1.38	$P<0.001$	1.21	$P<0.001$
Modena	1.38	$P<0.001$	1.04	$P=0.21$
Parma	1.02	$P=0.83$	1.22	$P<0.001$
Romagna	1.48	$P<0.001$	1.17	$P<0.001$
Turin	1.25	$P<0.001$	1.19	$P<0.001$

[a] The years analysed in prescreening and screening periods were those specified in Table 2.

seven Italian areas for women aged 40–79 years. Cases incident during the screening period were mostly diagnosed in the first 3-years after the beginning of the screening programme, therefore the study substantially evaluated the effect of the first screening round. The analysis was performed separately for every registry and in multivariate models pooling four registries (Ferrara, Florence, Modena and Parma). Some peculiarities of the other ones explained the insufficient fit of the pooled models with all registries (i.e. the very high percentage of unknown stages, due to a high proportion of cases being treated outside of the area covered by the registry, and the much lower incidence in Ragusa; the substantial increase of the population covered by cancer registration in the screening period in Romagna; the involvement in the screening programme, during the study period, of women in the age group of 50–59 years in Turin) and therefore their exclusion from the pooled analysis.

As a general rule, a registry would reach the definitive level of completeness several years after the incidence

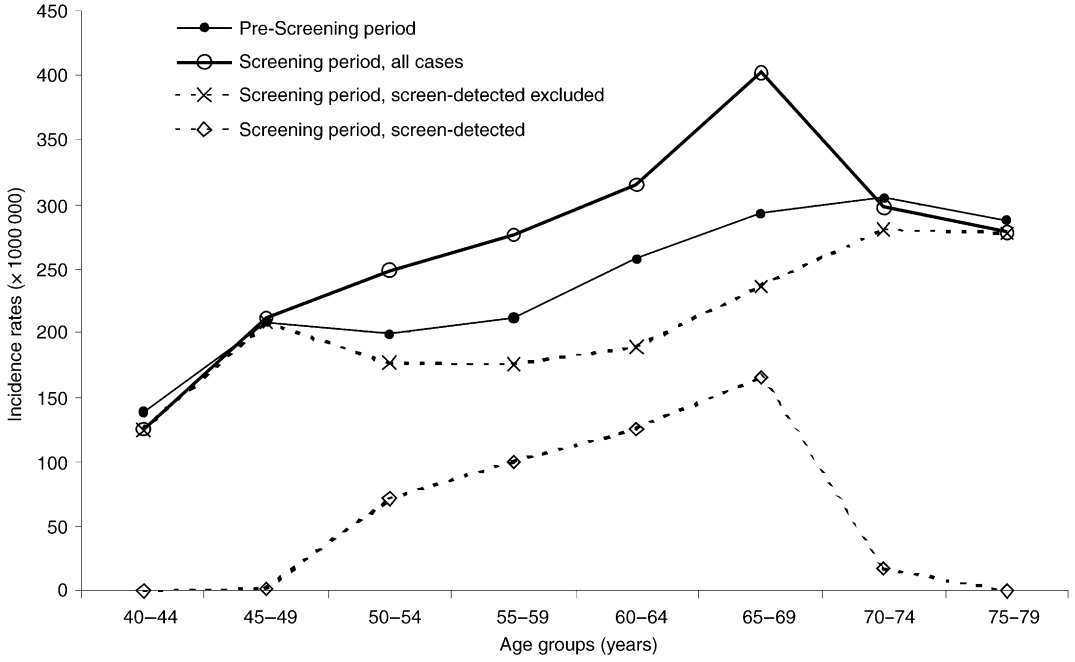

Fig. 1. Age-specific rates by period of screening for all invasive stages: pool of Ferrara, Florence, Modena and Parma registries; age 40–79 years.

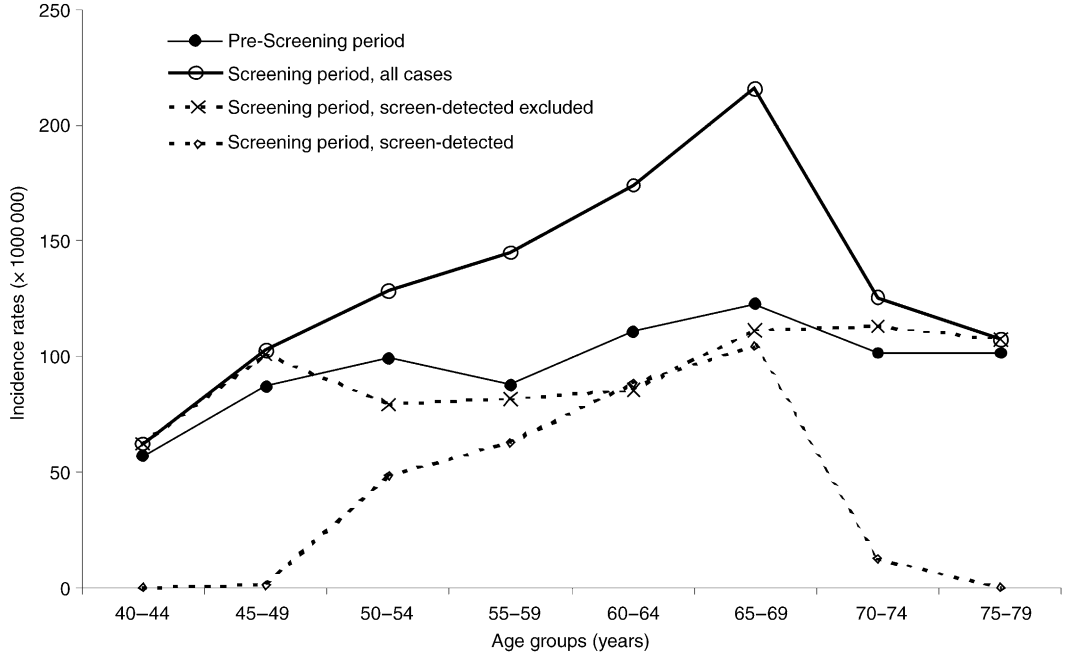

Fig. 2. Age-specific rates by period of screening for early cases: pool of Ferrara, Florence, Modena and Parma registries; age 40–79 years.

period. Therefore, the more recent data analysed (i.e. 1998, 1999) could potentially be affected by incompleteness, in particular for non-screen-detected cancers. The checking of case collections through computerised administrative data-sources (i.e. the hospital discharge recording system, developed at a national level since 1995 to finance hospital activities), carried out in the present study, ensured a good quality and non-biased completeness of cancer registration. Therefore, the cases included in the analysis, identified by qualified population-based cancer registries [14], can be considered to be fully representative of all those occurring in the resident population.

The study showed that the introduction of screening increased incidence rates of cancers of all stages and, in particular, of early cancers (and also of small invasive cancers and DCIS), the increase in the number of early cancers being partly due to 'spontaneous' early detection in ages outside of the screening programme. In addition, the screening modified the pattern of age-specific rates, with the maximum incidence peak at age 65–69 years, and caused a shift in diagnosis from the usual clinical services to a diagnostic screening activity among women aged 50–69 years.

Before the start of screening, the incidence rates for breast cancer were typical of an area at intermediate risk, with a significant, but not striking, geographical variability for registries located in Central-Northern Italy [14], while the incidence was much lower in the only registry located in Southern Italy. The low risk for breast cancers in Southern Italy is confirmed by current mortality data [15]. In all areas, independent of the baseline incidence, the introduction of screening increased incidence rates, both for all invasive cancers and, more markedly, for early cancers (screening/prescreening rate ratio ranging from between 1.07 and 1.47 and between 1.23 and 1.82, respectively). This early screening effect is expected and consistent with findings from previous studies [16–18]. As shown by regression models in the pooled analysis, the variable 'percentage of cases diagnosed at screening' totally explained the increased incidence of cancers of all stages. This variable is a proxy of the diffusion of the programme in the area, representing both the proportion of women invited and their compliance. Thus, this finding means that the increase in incidence is totally explained by screening. On the other hand, for 'early' cancers, an independent effect for the period of diagnosis (screening versus prescreening: +14%) persisted after adjustment for the percentage of cases diagnosed at screening. This independent effect for the period of diagnosis may be explained by the increase of early cases that also occurred in age groups that were not screened, as shown through the comparison of age-specific incidence rates before and during screening. A wide use of mammography as a preventive practice outside of screening programmes has been documented in several populations [19–22], and a screening-like effect of these practices on the stage-specific incidence rates has been suggested [16]. We feel that an effect due to stage classification bias on the incidence rate of early cases can be excluded. In fact, introducing in the model cases with an unknown stage, as well as the number of examined lymph nodes (as a proxy of the precision of stage definition) did not change the results.

The main short-term effects of a programme that is effective in reducing breast cancer mortality should be a reduction in the incidence of advanced cancer. Such a reduction can generally be expected after an increase during the prevalence screening round [8]. Our study, mostly limited to the first years after the beginning of screening, does not allow us to evaluate this aspect more closely, and further periods of incidence need to be analysed to evaluate the effectiveness of screening programmes in terms of a reduction in the incidence of advanced cancers at the population level. A moderate reduction in the second 3-year period after the start of screening was suggested in one registry (Florence), where a longer period of incidence data was available. A concomitant reduction of cases with an unknown stage could partially mask a more evident trend of advanced cases. A more detailed analysis of the Florence screening programme showed in invited women after the prevalence screening, a significant reduction (approximately a quarter) in the incidence of advanced carcinomas [23]. As concerns the effect of prevalence round of screening on advanced cancers, the results were not consistent across the registries for those aged 40–79 years. A more coherent picture was observed when the analysis was restricted to the screening age group (50–69 years). Indeed, nearly all registries showed an increasing trend in incidence. More information about the characteristics of screening programmes and the spontaneous widespread use of mammography before the start of screening (unavailable in the present study) are needed to explain the different effects on increase in advanced cancers. Nevertheless, some peculiarities with regard to the situation in Florence can be specified. Indeed, an organised screening programme, one of the first European experiences, was ongoing in some neighbouring rural municipalities since the beginning of the 1970s [24] and a clinic for early the diagnosis of breast cancer was active, the same centre carrying out both activities. It is presumed that this setting influenced the awareness of clinicians and women about early diagnosis, affecting the stage distribution before the start of screening programme.

In conclusion, the results showed, in a large series of well-defined population-based cases, that the increasing incidence of invasive breast cancers observed at the beginning of the screening is substantially an effect of the screening itself. As reported in other studies [25], it is

reassuring, from a public health perspective, that the increase in incidence of breast cancer is a consequence of the 'inflation' in diagnosis due to the detection of prevalent cases at the start of screening activity rather than the consequence of a 'true' increase in the background incidence. Furthermore, the study confirms the importance of cancer registries in monitoring the effect of breast cancer screening [16] and the validity, for this purpose, of the linkage between cancer registries and screening programmes databases [26]. In particular, only cancer registries provided incidence rates and stage distribution before the beginning of screening and a complete picture of incidence in the target population, while the linkage allows us to assess the impact at the population level of screening on breast cancer diagnosis.

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