Does an organised screening programme reduce the inequalities in breast cancer survival?

D. Puliti, G. Miccinesi, G. Manneschi, C. Buzzoni, E. Crocetti, E. Paci & M. Zappa

Clinical and Descriptive Epidemiology Unit, ISPO–Cancer Prevention and Research Institute, Florence, Italy

Background: The aim of the present study was to examine whether the implementation of an organised mammographic screening programme in Florence has been successful in reducing socioeconomic inequalities in breast cancer survival.

Patients and methods: All invasive breast cancer cases diagnosed in women resident in the city of Florence in a prescreening period and in the first 10 years of the screening programme were selected. Their socioeconomic status (SES) was determined by using the national census 2001 data. All breast cancers were followed up to 10 years after the diagnosis.

Results: In the prescreening period, the survival of deprived women was 12 percentage points lower than the reference class, both in the younger age class (<50 years old) and in the age class target of the screening programme (50–69 years old). This difference progressively decreases until disappearing completely during the first 10 years of the screening programme for the age class invited to screening, whereas it remains stable in the younger age class.

Participation in breast cancer screening and diagnostic accuracy were similar by SES.

Conclusion: The organised breast cancer screening implemented in the Florentine area achieved the goal of reducing inequalities in breast cancer survival.

Key words: breast cancer survival, screening programme, socioeconomic inequalities

Introduction

Strong evidence based on studies of different designs in a variety of populations and settings shows that cancer survival tends to be poorer in low compared with high socioeconomic groups [1–2]. Cancer stage at diagnosis and differences in treatment have been cited as the most important explanatory factors [3]. Other suggested factors of importance include individual patient characteristics such as comorbidity and psychosocial factors.

Socioeconomic gradients in cancer survival appear to be more pronounced in cancers with good prognosis, such as breast cancer for which tumour stage at diagnosis is an important prognostic factor [1, 4–5].

On the whole, survival of breast cancer patients has improved during the last 20 years but unfortunately not all groups of women share this benefit equally. Several studies, using individual and area-based socioeconomic measures, have consistently shown that deprived women with breast cancer have poorer survival [6–10].

Evidence of socioeconomic inequalities in cancer survival has been shown also in Italy [4, 11], a country with a National Health Care System that should provide equal access to health care.

Now, that the association between socioeconomic status (SES) and breast cancer survival seems to be established; the debate is no longer about whether inequalities exist but how can we deal with them. It has been suggested that the implementation of an organised screening programme based on equal access could represent an efficacious tool to redress social inequities in health [12]. However, controversial results have been reported in literature [13–14].

The aim of the present investigation is to examine whether the implementation of an organised mammographic screening programme in Florence has been successful in reducing socioeconomic inequalities in breast cancer survival.

Methods

Population study

The Florentine screening programme began in 1991, offering high-quality mammography every 2 years to all resident women aged 50–69 years [15]. The overall target population was ~60 000 with an attendance rate of ~60% at the prevalence round, which has increased to ~70% in recent years. Performance indicators including diagnosis and treatment are collected annually under a national survey carried out by the National Centre for Screening Monitoring [16].

Incidence and follow-up data were obtained from the Tuscan Cancer Registry, which has been operating in the area since 1985 and is member of the International Association of Cancer Registries [17].
In this analysis, we selected all invasive breast cancer cases diagnosed in women <70 years and resident in the city of Florence in a reference prescreening period (1985–1986) and in the first 10 years of the screening programme (1991–2000). We did not use the whole prescreening period (1985–1990) because the information about stage at diagnosis was not routinely collected in the Tuscan Cancer Registry. Cases incident in the years 1985–1986 had been revised for a specific study [18].

deprivation index
A deprivation index was constructed at national level to measure the relative socioeconomic disadvantage [19] by using the national census 2001 data. The index is available at the level of census section (~70 women for each section). The index synthesizes the socioeconomic information carried out by five indicators:

1) educational level (proportion of people with not more than primary education);
2) occupation (proportion of unemployed people);
3) housing condition (proportion of people living in rented house);
4) family condition (proportion of family with one parent only and dependant children) and
5) density (average number of people living in 100 m²).

In order to obtain a clear-cut contrast together with a stable reference class, we defined two socioeconomic classes using tertiles of the index distribution in the Florentine area:

a) reference class (first and second tertile) and
b) deprived class (third tertile).

The home address of each case at the date of diagnosis was available in the cancer registry and the census section was defined by a geographical reference procedure for each patient. The same geographical reference procedure was used for all the women registered in the computerised screening database in order to check for differential participation in breast cancer screening by SES.

detection method
All breast cancer cases were linked to the screening file and classified by a method of detection in five categories:

1) screen-detected cases;
2) cases diagnosed clinically within 30 months since a negative screening;
3) cases diagnosed clinically beyond 30 months since a negative screening;
4) cases diagnosed in women never respondent;
5) cases diagnosed in women not yet invited.

statistical analysis
All breast cancers were followed up at 31 December 2008 or at 10 years after the diagnosis. The follow-up information has been collected by the cancer registry, independently on the socioeconomic class and on the screening status, through linkage with the regional mortality registry and with the list of residents [20]. Breast cancer deaths were considered as failures and deaths other than breast cancer were censored.

Survival probability was estimated using the Kaplan–Meier method, whereas the hazard ratio (HR) and the confidence interval (CI) were estimated using the Cox model. The main factors included in the Cox model were age class (5 year), year of diagnosis (continuous), pathological T (1a, 1b, 1c, 2+, unknown) and pathological nodes (positive, negative, unknown). The assumption of proportionality of the hazard was tested by Schoenfeld residuals test [21].

The Freedman attributable proportion [22] was used to estimate the extent to which adjustment for the cancer stage accounted for differences in survival by socioeconomic group.

Because the completeness of the information about stage at diagnosis differs by SES and by calendar period, calculation was made of the proportion of advanced cancers as well as of the proportion of cases with stage II or more plus two-third of cases with unknown stage.

results
breast cancer survival by SES
In total, 2636 invasive breast cancer cases were considered for the survival analysis, with a total of 589 breast cancer deaths and 29 786 person-years, with a median follow-up time of 16.9, 14.2 and 9.6 years for incidence periods 1985–1986, 1991–1995 and 1996–2000, respectively.

The deprivation index was known for 2541 cases (missing 3.6%). The completeness level was almost the same in the three periods (missing: 4.3%, 3.1% and 3.9%, respectively; chi-squared test: P = 0.438). Deprived women had similar mean age at diagnosis as reference class women (55.4 and 54.9 years, respectively; P = 0.1619).

Table 1 shows 10-year breast cancer survival by SES stratifying for age class (<50 and 50–69 years) and for calendar period (1985–1986, 1991–1995 and 1996–2000). In the prescreening period (1985–1986), a large difference was observed in survival between the two socioeconomic classes both in <50-year-old women (Δ = 12%) as well in 50- to 69-year-old women (Δ = 12%). This difference remains stable in the younger age class for the entire study period, whereas it disappears in the age class invited to breast cancer screening.

Consistently, in the prescreening period, the proportion of advanced cancers (defined as all cases with stage II or more at diagnosis plus two-third of cases with unknown stage) was larger among deprived women in both age classes (being 68% versus 62% in the younger age class and 68% versus 61% in the 50- to 69-year-old women). After the introduction of the screening programme, the difference remains stable in the younger age class (65% versus 56%), whereas it decreases strongly in the screening age class (51% versus 50%).

In order to clarify the possible explanatory factors of the reduced survival in deprived women, we fitted a Cox model to estimate the HRs of deprived versus reference women adjusted for the main confounding factors (age and year at diagnosis) and for the stage at diagnosis (pathological T and pathological nodes) separately for each age class and period (Table 2). In the prescreening period, deprived women of both age classes showed an excess risk of breast cancer death of ~40% which approximately reduces by half after adjusting for cancer stage. In the screening period, the excess risk seems to increase further for the younger age class, whereas it disappears in women invited to screening. The Freedman estimate of the proportion of the SES effect attributable to cancer stage in the prescreening period was 42% and slightly reduced to 36% in the screening period.

attendance rate by SES
The information about deprivation index for the women invited to breast cancer screening in the city of Florence was available at a level of completeness of 97% (~460 000 invitations). The average compliance to the invitation was equal to 67% for deprived women and 70% for the women in the reference class. Table 3 reports the coverage of mammographic screening by
In order to evaluate if inequalities in breast cancer survival have been reduced by the implementation of an organised screening programme in the Florentine area, we compared 10-year breast cancer survival by SES in the prescreening (1985–1986) and in the first 10 years of the screening programme (1991–1995, 1996–2000). In the prescreening period, deprived women had 12% lower survival as compared with reference class, both in the younger age class (<50 years old) and in the age class target of the screening programme (50–69 years old). This difference progressively decreases until disappearing completely during the first 10 years of the screening programme for the age class invited to screening, whereas it remains stable in the younger age class.

In order to clarify the possible explanatory factors of the reduced breast cancer survival in deprived women, we took into account the impact on survival of cancer stage at diagnosis. By the Freedman statistics, we estimated that the proportion of the socioeconomic difference observed in breast cancer survival attributable to cancer stage ranged between 42% and 36% in the two periods (prescreening and screening). These are probably underestimates because of the residual confounding factors in the adjustment for pathological T and nodes. Anyway, as widely reported in scientific literature [3, 7], these results suggest that differences in cancer survival by SES depend not only on the timing of the diagnosis but also on the type and quality of treatment provided. Since the hazard of breast cancer death in deprived and reference women becomes equal after 10 years of screening programme, it is likely that the introduction of the screening programme determines an improvement both in time at diagnosis and in quality of treatment in the lower socioeconomic class [23].

A key point for socioeconomic analysis is the choice of a deprivation index accurate and able to discriminate. Three possible limitations are considered for our definition of SES. First, we based the definition of the SES on an ecological measure of deprivation, constructed on the basis of the characteristics of the small area (on average 70 women) in which each patient was resident at the time of diagnosis. The expected effect of using an aggregate measure, rather than an individual one, is a trend towards the null hypothesis, meaning a dilution effect tending to attenuate the survival gradient. This could have happened in our study but it cannot explain the different survival temporal trend observed in the two age classes. Secondly, the possibility that our definition of the socioeconomic contrast (first and second tertile versus third tertile) may have weakened the survival differential cannot be excluded but, as above, it cannot explain the different survival trend. Thirdly, we used a deprivation index constructed using national 2001 census data assuming that it has sufficient temporal stability in the area and period under consideration.

### Table 1. Ten-year breast cancer survival and (95% confidence intervals) by socioeconomic status stratified for age class and calendar period

<table>
<thead>
<tr>
<th>Reference class</th>
<th>Deprived class</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
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<tr>
<td>&lt;50 years old</td>
<td></td>
</tr>
<tr>
<td>1985–1986</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>82 (72–89)</td>
</tr>
<tr>
<td>1991–1995</td>
<td>189</td>
</tr>
<tr>
<td></td>
<td>82 (76–87)</td>
</tr>
<tr>
<td>1996–2000</td>
<td>204</td>
</tr>
<tr>
<td></td>
<td>88 (82–91)</td>
</tr>
<tr>
<td>50–69 years old</td>
<td></td>
</tr>
<tr>
<td>1985–1986</td>
<td>189</td>
</tr>
<tr>
<td></td>
<td>64 (57–71)</td>
</tr>
<tr>
<td>1991–1995</td>
<td>552</td>
</tr>
<tr>
<td></td>
<td>81 (77–84)</td>
</tr>
<tr>
<td>1996–2000</td>
<td>537</td>
</tr>
<tr>
<td></td>
<td>86 (82–89)</td>
</tr>
</tbody>
</table>

- Differences are calculated before rounding of the values.

For BC, breast cancer.

### Table 2. Hazard ratios (HRs) and (95% confidence intervals) of deprived versus reference women stratified for age class and calendar period

<table>
<thead>
<tr>
<th></th>
<th>HR adjusted for age and year</th>
<th>HR adjusted for age, year, pT and pN</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 years old</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1985–1986</td>
<td>1.45 (0.54–3.87)</td>
<td>1.28 (0.45–3.67)</td>
</tr>
<tr>
<td>1991–1995</td>
<td>1.71 (1.05–2.79)</td>
<td>1.34 (0.81–2.22)</td>
</tr>
<tr>
<td>1996–2000</td>
<td>1.95 (1.09–3.49)</td>
<td>2.02 (1.12–3.63)</td>
</tr>
<tr>
<td>50–69 years old</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1985–1986</td>
<td>1.36 (0.91–2.04)</td>
<td>1.16 (0.76–1.77)</td>
</tr>
<tr>
<td>1991–1995</td>
<td>1.22 (0.87–1.70)</td>
<td>1.13 (0.81–1.58)</td>
</tr>
<tr>
<td>1996–2000</td>
<td>0.98 (0.63–1.53)</td>
<td>1.08 (0.68–1.70)</td>
</tr>
</tbody>
</table>

pT, pathological T; pN, pathological nodes.

SES (the coverage was defined as the proportion of women who carried out at least one screening test among the women invited to three subsequent rounds). Consistently with compliance results, the coverage of mammographic screening in the two socioeconomic classes differs only by 2–3 percentage points.

### Diagnostic Accuracy by SES

In Table 4, breast cancer cases diagnosed in women 50–69 years old in the screening period are presented by detection modality and SES. In total, 44.5% of cases were detected at the screening, 14.3% and 2.9% were detected in women screened with negative results (respectively within and beyond 30 months from the screening test), 22.6% in women never respondent and 15.7% in women not yet invited. The detection modality distribution does not differ between the two socioeconomic classes (chi-squared test: P = 0.855). The odds ratio of screen detected for deprived versus reference women is 0.96 (95% CI 0.69–1.33).

### Discussion

In order to evaluate if inequalities in breast cancer survival have been reduced by the implementation of an organised screening programme in the Florentine area, we compared 10-year breast cancer survival by SES in the prescreening (1985–1986) and in the first 10 years of the screening programme (1991–1995, 1996–2000). In the prescreening period, deprived women had 12% lower survival as compared with reference class, both in the younger age class (<50 years old) and in the age class target of the screening programme (50–69 years old). This difference progressively decreases until disappearing completely during the first 10 years of the screening programme for the age class invited to screening, whereas it remains stable in the younger age class.

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Table 3. Coverage* of mammographic screening [(proportion (%) and 95% confidence interval)] by socioeconomic status

<table>
<thead>
<tr>
<th>Deprivation index</th>
<th>1st, 2nd, 3rd rounds</th>
<th>4th, 5th, 6th rounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference class</td>
<td>73.8 (75.2% to 76.3%)</td>
<td>82.2 (81.7% to 82.6%)</td>
</tr>
<tr>
<td>Deprived class</td>
<td>73.4 (72.6% to 74.1%)</td>
<td>80.0 (79.3% to 80.7%)</td>
</tr>
</tbody>
</table>

*The coverage was defined as the proportion of women who carried out at least one screening test among the women invited to three subsequent rounds.

Table 4. Breast cancer cases [n (%)] by detection modality and socioeconomic status

<table>
<thead>
<tr>
<th>Detection modality</th>
<th>Reference class</th>
<th>Deprived class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen detected</td>
<td>489 (44.9)</td>
<td>199 (43.5)</td>
</tr>
<tr>
<td>Screened (within 30 months)</td>
<td>155 (14.2)</td>
<td>66 (14.4)</td>
</tr>
<tr>
<td>Screened (beyond 30 months)</td>
<td>33 (3.0)</td>
<td>11 (2.4)</td>
</tr>
<tr>
<td>Never respondent</td>
<td>247 (22.7)</td>
<td>103 (22.5)</td>
</tr>
<tr>
<td>Not yet invited</td>
<td>165 (15.2)</td>
<td>78 (17.1)</td>
</tr>
<tr>
<td>Total</td>
<td>1089 (100)</td>
<td>457 (100)</td>
</tr>
</tbody>
</table>

$\chi^2 = 1.34, P = 0.855.$

Some evidence of this is provided by a recent statistical analysis conducted in Tuscany at municipality level [24]. Anyway, the use of 2001 census data to determine the deprivation index might well represent the SES conditions of the cases diagnosed in the 1995–2000 but it is definitively less accurate for cases diagnose previously, especially for cases diagnosed in 1985–1986. Misclassification of SES could have occurred in both directions (deprived women might be incorrectly classified in the reference class and vice versa) but it is most likely that misclassification would not have depended from the outcome under study (breast cancer survival). Therefore, the misclassification between deprived and not deprived women could have lead to a bias towards the null hypothesis, which means a possible underestimation of survival difference observed in the prescreening period (1985–1986).

The use of survival in order to evaluate the screening effect on socioeconomic inequalities could be criticised on the basis of the potential dilution effect caused by the detection of nonlethal cancers by screening. Indeed, if screening would detect more nonlethal cancers, the difference in survival among socioeconomic classes could be diluted. This problem could not have been prevented by analysing mortality rates instead of survival because of the known association between SES and incidence—women of high socioeconomic class tend to have higher breast cancer incidence as compared with low socioeconomic classes—as well as between SES and survival rates (in the opposite direction). Since mortality rates depend on both incidence and survival, the association between SES and mortality would be difficult to be interpreted. On the other hand, we believe that the dilution effect on survival due to nonlethal cancers cannot explain the fact that survival differences disappear completely during the first 10 years of the screening programme. Since the proportion of screen-detected women is nearly equal in the two socioeconomic classes (45% and 44%), it is very likely that the proportion of overdiagnosis and slow-growing tumours will be the same in the two classes. If we would assume an increased incidence of 10% in both classes—entirely due to nonlethal cancers—the observed 12% survival difference would become 11%. Assuming a more extreme and improbable scenario (increased incidence of 50%), the difference would reduce to 8%. Therefore, the potential dilution effect cannot explain, but minimally, our results.

It is clear that the necessary condition for a new health intervention to reduce inequalities is that all target population be equally covered including subjects with a lower SES. Health inequalities will diminish when the higher SES will have achieved new minimum achievable levels for morbidity and mortality—beyond which substantial further improvements are unlikely occur—and when the lower class reaches the same level of access to the intervention [25]. Indeed, our data show that both compliance to invitation and coverage of mammographic screening are similar by SES. These screening attendance indicators are slightly lower than those reported in north European countries but they do not differ by SES as in those countries [26–27]. Furthermore, the proportion of cases detected at screening is almost the same by SES, suggesting that the diagnostic accuracy is similar in deprived and reference class.

All scientific literature consistently shows that breast cancer survival differ by SES. Only a few studies deal with the possible impact of a screening programme on these differences, directly or indirectly, whereas many more describe the differences in participation in breast screening programme by SES. As far as we know, no studies have considered the impact of a screening programme on socioeconomic variation in survival together with the differences in participation and diagnostic accuracy by SES.

In a study carried out in UK [14], starting from the observation that the risk of advanced cancers for deprived women as compared with most affluent women is slightly higher in the age group eligible for screening than in the age group not eligible for screening, it has been suggested that the national screening programme may have led to an increase of inequalities. The reported difference does not seem to be statistical significant. Furthermore, the study does not take into account if the compliance rate to invitation was similar by SES.

In a population-based study, conducted in a country with a long-lasting screening programme, breast cancer survival was compared by SES stratifying by age class [28]. The authors found that the social difference was more pronounced in the younger age groups, particularly among women <50 years at diagnosis. No association with the screening programme was suggested by the authors but these results can be considered consistent with ours.

Recently, Palencia et al. [29] described inequalities in the use of breast cancer screening service according to educational level in European countries and found that these inequalities are higher in countries without organised cancer screening programmes. These results underline the potential benefits of population-based screening programmes.

As far as we know, the only study evaluating the impact of mammographic screening on survival according to SES is the study conducted by Louwman [13] in the Netherlands. The study...
design is similar to ours but the results are the opposite: in the prescreening period survival rates did not differ among socioeconomic classes, but since the introduction of screening, the survival of women with a high SES has improved more than that for low socioeconomic classes. These striking results could be explained by two methodological limits of the study: the authors considered overall survival (rather than cause-specific survival) and used two different socioeconomic indexes for prescreening and screening periods. The index used in the prescreening period seems to be biased being based on self-reported data. Indeed, it is not able to detect the expected survival differences between socioeconomic classes. Furthermore, the study did not verify whether compliance to invitation was similar by SES. We think that the similar participation by SES, observed in the Florentine organised cancer screening together with the use of cause-specific survival, explains the different results of our analysis.

In conclusion, the organised breast cancer screening programme implemented in the Florentine area achieved the goal of reducing socioeconomic inequalities in breast cancer survival. The key role to achieve this was played by the similar participation in the higher and lower socioeconomic classes.

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disclosure
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references