Evaluation of service mammography screening impact in Italy. The contribution of hazard analysis

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In Europe, at the end of the 1980s and in the early 1990s, many aged 50 to 69 years.13 The evidence has been challenged registry has been active, collecting information on all the screening has been provided, a population-based cancer screening programmes that conform with European guide-

1. Introduction

In Europe, at the end of the 1980s and in the early 1990s, many countries implemented breast cancer service screening as public health programmes offering periodic mammography by invitation to women aged 50 to 69 (or 64).1

In Italy, pilot projects have been active in Florence and Turin since the early 1990s,2 and since 1995 several areas (in northern and central regions) have started service screening programmes that conform with European guidelines.3 The Italian group for mammography screening (GISMA) was established in 1990 to improve the quality of service screening programmes, and to compare early indicators of performance.4 In the majority of the areas where service screening has been provided, a population-based cancer registry has been active, collecting information on all the incident breast cancer cases and assuring their follow-up for vital status.5

The most important aim of breast cancer screening programmes is to reduce breast cancer specific mortality in the target population. Service mammography screening is a process, starting with 2-view, high quality mammography and continuing with diagnosis and treatment; each step is essential to achieve the expected result. The screening test should be sensitive enough to detect the cancer early in the natural history of the disease (the diagnostic phase), and the treatment of early lesions should be effective so that the prognosis of the disease is modified (the therapeutic phase).

In a number of randomised clinical trials (RCTs) started in the 1970s, breast cancer screening of post-menopausal women has been shown to be effective for reducing breast cancer mortality.6–12 Screening mammography reduces breast cancer mortality by about 20% to 35% in women aged 50 to 69 years.13 The evidence has been challenged in several publications,14,15 but the majority of scientific agencies have confirmed the potential benefit of periodic mammography.16

The challenge today is to show the impact of service screening programmes on breast cancer specific mortality in the communities where screening is on-going.17

Methodology to evaluate the mortality reduction achieved by a screening programme in a target population has been suggested and applied in the evaluation of service screening.18,19 In the evaluation of survival experience, the analysis is not based on the target female population, but rather on the breast cancer cases which were diagnosed in the population immediately before and after the start of a breast cancer screening programme. There are significant problems in evaluating service screening using survival rates as the major parameter of outcome instead of mortality rates (the endpoint of interest in randomised clinical tri-

2. Materials and methods

All population-based breast cancers diagnosed in women aged 50–69 years, resident in nine areas where a screening programme was active (Torino, Parma, Reggio-Emilia, Ferrara, Modena, Bologna, Romagna, Firenze and Perugia) and which participated in the IMPACT study21 were included. ‘Death certificate only’ cases (DCO) were excluded. IARC rules for cancer registration were adopted.5 All cases were linked to the screening file and categorised by detection method. Additionally, cases were split into screen-detected (SD) and not screen-detected (NSD) divisions, and, further, cases in the NSD division were divided so that there were four main case-divi-

1) Having a tumour detected in the first or subsequent round at the first screening test (i.e. tumours detected in prevalence screening) and cases having a tumour detected at a repeated screening test (i.e. tumours detected in incidence screening),
Not screen-detected (NSD) cases
2) Diagnosed clinically outside the screening process following a negative screening test (includes interval cancer cases),
3) Diagnosed in those women who never responded to their invitation – the ‘never-respondent’ case-division,
4) Diagnosed before an invitation could be sent (as, typically, it takes several years to achieve full coverage of the population with an invitation to screening) – the ‘not-yet invited’ case-division.

In this paper we refer to the cases in 4) as the non-invited group and those in 1), 2) and 3) as the invited group.

2.1 Survival analyses

All breast cancer cases, diagnosed from the year before the start of the local screening programme to the year 2001 and categorised by detection modality, were followed up at 31st December 2005 or at 10 years after the diagnosis. The follow up information has been collected by the cancer registries, independently of the screening status, through linkage with the regional mortality registry and with the list of residents. Breast cancer deaths were considered as failures and deaths other than breast cancer were censored. In situ carcinomas and multiple primaries were excluded from the survival analysis.

For each woman the date of the invitation to attend for screening mammography defines the before and after epochs, and the woman is grouped as either non-invited or invited. The analysis is by intention-to-screen, and so the subjects are considered as invited independently of their attendance.

In order to assess the contribution of lead time on survival, a time dependent analysis was performed using 5-year intervals. In the absence of any effective treatment, subjects detected at screening would lose, after the period of diagnostic anticipation (i.e. the lead time), the only apparent benefit, and cause-specific death would be neither postponed nor avoided. Assuming 3–4 years to be an average lead-time for screen-detected breast cancer cases, if after 10 years of follow-up survival rates of screen-detected cases were equal to or clearly converging towards those observed in the non-screened, the benefit of survival due to diagnostic anticipation would not represent a real benefit in terms of actual mortality reduction. The comparison of hazards in the second 5-year period is almost completely free from the lead time bias if proportional hazard is given.

In order to take into account the possibility of length-biased sampling, which is the main component of overdiagnosis, we estimated the hazard ratios adjusted for the tumour characteristics. The detection at screening of indolent breast cancers or cases with extremely low - or absent - aggressiveness is considered a possible, important side-effect of screening. If the adjusted hazard ratios were close to 1 then we could exclude any important role of length bias in determining the observed survival benefit. Due to the association between age class and length bias, we performed this adjusted analysis separately by age class.

Survival probability was estimated using the Kaplan–Meier method, and the hazard ratio and confidence interval were estimated using the Cox model. The main factors included in the Cox model were the pathological T (1 a, b & c; 2+; unknown), pathological nodes (positive, negative, unknown) and grading (1, 2, 3, unknown), year of diagnosis and registry.

The assumption of proportionality of the hazard was tested following Grambsch and Therneau and based on scaled Schoenfeld residuals. A kernel-smoothed hazard estimate was obtained using the cumulative hazard function and a time bandwidth of 4 years.

3. Results

In total 14,262 breast cancer cases emerged from 4,297,934 person years in the nine screening areas (age-specific incidence rates: 2.99, 3.09, 3.36 and 3.87 per 1000 person years respectively in the 50–54, 55–59, 60–64 and 65–69 age groups). In Table 1 breast cancer cases are presented by detection modality and tumour characteristics. In total 37% of cases were detected at screening (prevalence or incidence). 8.1% were detected in women screened with negative results, and are subdivided by time since the last negative test (< 2 years of interval, >2 years). There was a higher proportion of in situ and early breast cancer in screen-detected cases by pathological T, nodal status and grading than in non-screen-detected (64.3% versus 40.7%, p < 0.0001). The nodal status of the cases in the not-screen-detected, never-respondent and not-yet invited case-divisions were similar.

Invasive breast cancers (N = 12,987 ) were considered for the survival analysis, for a total of 1921 breast cancer deaths and 85,422 person-years, with a median follow-up time of 6.6 years. 5570 cases were grouped as non-invited and 7417 as invited. 88 invasive cancers with unknown cause of death were not considered in the survival analysis.

In Fig. 1 the Kaplan–Meier survival curves of invasive cases are compared by invitation status, showing at 10 years after diagnosis a survival rate of 85.3% for the invited group against 75.6% for the non-invited. There was an excess of breast cancer deaths for the non-invited of 9.7%, with a statistically significant log rank test (p <0.001).

In Fig. 2 survival data are presented by detection modality, showing a higher survival rate for screen-detected breast cancers and a lower rate for the never-respondent. The log rank test using non-invited as the reference category was statistically significantly different for screen-detected (p < 0.001) and never-respondent (p = 0.007). The median follow-up was 7.5 for the non-invited cases and 6.1 for the invited cases (6.3 years for screen-detected cases).

In Fig. 3 the survival curves for the invited versus the non-invited groups by 5-year age-groups (age at diagnosis) were plotted showing an increasingly greater benefit by age, in particular 65 years and older. The 10-year survival rate difference was 6.3%, 9.2%, 9.3% and 12.7% for cases aged 50–54, 55–59, 60–64 and 65–69 respectively. The larger benefit in older women is mainly because the 10-year survival in non-invited was lower.

In Fig. 4 the hazards are shown over time for non-invited and invited groups, respectively, by 5-year age-group. The pattern of the hazard over time for the invited group is almost
Table 1 – Breast cancer cases by detection modality and tumour characteristics

<table>
<thead>
<tr>
<th>Invited group</th>
<th>SD Prevalence</th>
<th>SD Incidence</th>
<th>Interval cases</th>
<th>Never respondent</th>
<th>Total Invited</th>
<th>Non-invited</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;= 2 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cases</td>
<td>3910</td>
<td>1420</td>
<td>874</td>
<td>282</td>
<td>1828</td>
<td>8314</td>
<td>5948</td>
</tr>
<tr>
<td>%</td>
<td>27</td>
<td>10</td>
<td>6.1</td>
<td>2</td>
<td>13</td>
<td>58</td>
<td>42</td>
</tr>
<tr>
<td>pT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT1s</td>
<td>517 (13)</td>
<td>195 (14)</td>
<td>58 (7.6)</td>
<td>26 (9.2)</td>
<td>101 (5.5)</td>
<td>897 (11)</td>
<td>378 (6.4)</td>
</tr>
<tr>
<td>pTm1cr</td>
<td>88 (2.3)</td>
<td>32 (2.3)</td>
<td>11 (1.3)</td>
<td>1 (0.4)</td>
<td>34 (1.9)</td>
<td>166 (2.0)</td>
<td>77 (1.3)</td>
</tr>
<tr>
<td>pT1a</td>
<td>256 (6.6)</td>
<td>119 (8.4)</td>
<td>39 (4.5)</td>
<td>9 (3.2)</td>
<td>61 (3.3)</td>
<td>484 (5.8)</td>
<td>165 (2.8)</td>
</tr>
<tr>
<td>pT1b</td>
<td>990 (25)</td>
<td>365 (26)</td>
<td>118 (14)</td>
<td>53 (19)</td>
<td>220 (12)</td>
<td>1746 (21)</td>
<td>802 (14)</td>
</tr>
<tr>
<td>pT1c</td>
<td>1416 (36)</td>
<td>514 (36)</td>
<td>353 (40)</td>
<td>100 (36)</td>
<td>577 (32)</td>
<td>2960 (36)</td>
<td>2108 (35)</td>
</tr>
<tr>
<td>pT1 nS</td>
<td>6 (0.2)</td>
<td>1 (0.1)</td>
<td>3 (0.3)</td>
<td>1 (0.4)</td>
<td>7 (0.4)</td>
<td>18 (0.2)</td>
<td>16 (0.3)</td>
</tr>
<tr>
<td>pT2+</td>
<td>580 (15)</td>
<td>173 (12)</td>
<td>250 (29)</td>
<td>79 (28)</td>
<td>662 (36)</td>
<td>1744 (21)</td>
<td>1940 (33)</td>
</tr>
<tr>
<td>Unknown</td>
<td>57 (1.5)</td>
<td>21 (1.5)</td>
<td>42 (4.8)</td>
<td>13 (4.6)</td>
<td>166 (9.1)</td>
<td>299 (3.6)</td>
<td>462 (7.6)</td>
</tr>
<tr>
<td>pN*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pN0</td>
<td>2289 (68)</td>
<td>786 (64)</td>
<td>438 (54)</td>
<td>143 (56)</td>
<td>800 (46)</td>
<td>4456 (60)</td>
<td>2793 (50)</td>
</tr>
<tr>
<td>pN+</td>
<td>866 (26)</td>
<td>305 (25)</td>
<td>311 (38)</td>
<td>96 (38)</td>
<td>670 (39)</td>
<td>2248 (30)</td>
<td>2062 (37)</td>
</tr>
<tr>
<td>Unknown</td>
<td>238 (7.0)</td>
<td>134 (11)</td>
<td>67 (8.2)</td>
<td>17 (6.6)</td>
<td>257 (15)</td>
<td>713 (9.6)</td>
<td>715 (13)</td>
</tr>
<tr>
<td>Grading*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good (I)</td>
<td>900 (27)</td>
<td>335 (27)</td>
<td>123 (15)</td>
<td>48 (19)</td>
<td>220 (13)</td>
<td>1626 (22)</td>
<td>707 (13)</td>
</tr>
<tr>
<td>Moderate (II)</td>
<td>1343 (40)</td>
<td>497 (41)</td>
<td>290 (36)</td>
<td>73 (29)</td>
<td>604 (35)</td>
<td>2807 (38)</td>
<td>1864 (34)</td>
</tr>
<tr>
<td>Poor (III)</td>
<td>609 (18)</td>
<td>256 (21)</td>
<td>250 (31)</td>
<td>89 (35)</td>
<td>503 (29)</td>
<td>1707 (23)</td>
<td>1413 (25)</td>
</tr>
<tr>
<td>Unknown</td>
<td>541 (16)</td>
<td>137 (11)</td>
<td>153 (19)</td>
<td>46 (18)</td>
<td>400 (23)</td>
<td>1277 (17)</td>
<td>1586 (29)</td>
</tr>
<tr>
<td>No invasive cases</td>
<td>3393</td>
<td>1225</td>
<td>816</td>
<td>256</td>
<td>1727</td>
<td>7417</td>
<td>5570</td>
</tr>
<tr>
<td>Breast cancer deaths</td>
<td>202</td>
<td>66</td>
<td>115</td>
<td>36</td>
<td>351</td>
<td>770</td>
<td>1151</td>
</tr>
</tbody>
</table>

a Only invasive cases.
the same in all age-groups (50 to 69) – always below 20 per 1000. The hazard had a different pattern by age in the non-invited group, with the lowest level immediately after the diagnosis in women aged 50–59 years at diagnosis. In older women the hazard was higher at approximately 40 per 1000 in the first years after diagnosis and rapidly decreasing after a few years of follow-up.

In order to assess the contribution of lead time on survival benefit of invited versus non-invited cases, a time dependent analysis was performed using two time windows - (0–5) and [5–10] years after diagnosis. The crude hazard ratios for the invited versus non-invited are presented by time window in Table 2. For the 50–54, 55–59 and 60–64 age groups the hazard ratios were similar in the two time windows and the proportionality test for the whole 10-years period was never statistically significant. For the 65–69 age-group the proportionality test for the whole study period was statistically significant and the hazard ratios were 0.37 and 0.63, respectively in the (0–5) and [5–10] year time windows. The Cox survival analysis was applied by 5-year age-group and the adjustment for tumour characteristics (pathological T, nodal status and grading) was used to evaluate how much of the survival benefit was explained by diagnostic anticipation (Table 2). For the three younger age groups the adjusted hazard ratios were close to 1 in both time windows. For 65–69 year old women the hazard ratios were 0.65 and 0.92, respectively in the (0–5) and [5–10] year time windows.

4. Discussion

Measurement of the reduction of breast cancer mortality in a target population is the proper evaluation of the impact of service screening, i.e. the additional benefit in breast cancer mortality attributable to the screening programme. This is achievable with several methodological approaches, for example, case-control studies or incidence-based mortality analysis. The most recent incidence-based mortality studies indicate a reduction in breast cancer mortality of 22% among...
the invited women and of 45% among women actually screened.

Survival rates, measured within population-based breast cancer cases among invited and not invited women, are potentially biased estimates of the benefit given the distortions due to lead time and length bias.

In the IMPACT study the invited cases showed, at 10 years, a statistically significant 9.7% improved survival rate over the non-invited. Survival rates by method of detection presented a higher survival rate for screen-detected cases over time, and the survival rate for never-respondent women showed a statistically significant difference from the survival rate in the non-invited, i.e. the control group.

In the absence of the practical efficacy of screening, the screen-detected breast cancer cases have a survival benefit due only to lead time. In this case, as time passes, the hazard of the invited cases moves towards and meets that of the non-invited cases, entirely eliminating the only apparent survival benefit. In a time-dependent survival analysis of 20 years of follow-up from the Swedish Two-County Study it has been shown that the effect of tumour characteristics has a lasting influence on subsequent survival, albeit attenuated in later years. Consistently, in the IMPACT study, the analysis of the hazard comparing breast cancer cases diagnosed in invited and not invited women (on an intention-to-screen analysis) showed that the benefit 10 years after the diagnosis was not lost.

The analysis by age-group showed important differences by 5-year age-groups. The survival benefit was higher in older women, and particularly in the 65–69 year age-group. In all age-groups the hazards of invited women were very similar and stable, maintaining a low level of the hazard over time (under 20 per 1000) and across both time windows. In non-invited cases, the hazards were different by age-group and time window. In the younger age-groups (50–54 and 55–59) the pattern was comparable to that of the invited cases, although with higher values (always over 20 per 1000). In older (60 and over) non-invited women the hazard falls down immediately after the diagnosis, a pattern over time which was completely lost in the invited cases. A possible explanation of these differences between younger and older women is the different exposure by age-group to spontaneous practices of

![Fig. 4 – Hazard by 5-year age-group at diagnosis and invitation status.](image)

**Table 2 – Crude and adjusted hazard ratios for invited versus non-invited women in 5-year age group**

<table>
<thead>
<tr>
<th>Age class</th>
<th>Time window (years)</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>Adjusted Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>50–54</td>
<td>[0 – 5]</td>
<td>0.65</td>
<td>0.52 – 0.83</td>
<td>1.04</td>
<td>0.81 – 1.33</td>
</tr>
<tr>
<td></td>
<td>[5 – 10]</td>
<td>0.68</td>
<td>0.45 – 1.02</td>
<td>1.00</td>
<td>0.65 – 1.52</td>
</tr>
<tr>
<td>55–59</td>
<td>[0 – 5]</td>
<td>0.61</td>
<td>0.49 – 0.75</td>
<td>1.04</td>
<td>0.83 – 1.30</td>
</tr>
<tr>
<td></td>
<td>[5 – 10]</td>
<td>0.55</td>
<td>0.38 – 0.78</td>
<td>0.88</td>
<td>0.60 – 1.28</td>
</tr>
<tr>
<td>60–64</td>
<td>[0 – 5]</td>
<td>0.53</td>
<td>0.43 – 0.65</td>
<td>0.87</td>
<td>0.70 – 1.08</td>
</tr>
<tr>
<td></td>
<td>[5 – 10]</td>
<td>0.73</td>
<td>0.51 – 1.05</td>
<td>1.09</td>
<td>0.74 – 1.60</td>
</tr>
<tr>
<td>65–69</td>
<td>[0 – 5]</td>
<td>0.37</td>
<td>0.30 – 0.45</td>
<td>0.65</td>
<td>0.52 – 0.81</td>
</tr>
<tr>
<td></td>
<td>[5 – 10]</td>
<td>0.63</td>
<td>0.44 – 0.90</td>
<td>0.92</td>
<td>0.63 – 1.35</td>
</tr>
<tr>
<td>50–69</td>
<td>[0 – 5]</td>
<td>0.52</td>
<td>0.47 – 0.58</td>
<td>0.87</td>
<td>0.76 – 0.99</td>
</tr>
<tr>
<td></td>
<td>[5 – 10]</td>
<td>0.64</td>
<td>0.53 – 0.78</td>
<td>0.96</td>
<td>0.77 – 1.21</td>
</tr>
</tbody>
</table>
mammography screening of non-invited women. Before the start of the organised programme (that is, in the absence of service screening) younger women attended mammography screening more than older women. After the start of the programme the compliance rate of 50–69 year old women to screening mammography was approximately 65% against less than 20% in the pre-screening epoch, and both showed a decreasing trend by age.31

The survival benefit observed in 50–64 year old women was almost completely explained by the more favourable tumour characteristics. After adjustment by the Cox model for pathological T, nodal status and grade, the hazard ratio was close to unity showing that the whole survival benefit for the invited was attributable to the shift of cancer gravity characteristics. In the 65–69 year old women at diagnosis, a residual, statistically significant, extra benefit after adjustment for tumour characteristics was evident in the (0–5) year time window. This extra benefit is attributable to residual lead time and/or length bias.

The detection of slow growing cases, but not necessarily less aggressive when clinically symptomatic, could also explain the excess of incidence observed in this age-group which we have shown in a previous paper.26 When evaluating the risk of overdiagnosis in the IMPACT dataset we reported an excess of incidence of 5.7%, including carcinoma in situ in 65–69 year old women, whereas among 50–64 year olds our estimate of over-diagnosis was 2.3%. A recent systematic review on estimates of invasive breast cancer overdetection concluded that the least biased estimates of over-detection are those obtained by using data from a randomised clinical trial in which there are more than several years of follow-up after screening stops and the control group is never screened.32 Zackrisson33 and Moss34 were the only authors to use this method and their estimates ranged from 1.7% to 8% according to the age at diagnosis.

Joensuu35 analysed tumour characteristics of breast cancer cases in Finland showing statistically significant differences in distant disease-free survival between cases detected at screening or outside of screening. In multivariate survival analysis taking into account tumour characteristics and age at diagnosis they showed detection at screening was an independent prognostic factor. Shen and colleagues36 evaluated the role of detection method in predicting breast cancer survival by analysing the data of the Health Insurance Plan and Canadian Breast Cancer Screening Studies, adjusting for tumour size, nodal status and disease stage and age at diagnosis. They have found method of detection as an important prognostic factor for breast cancer survival, beyond stage shift. Based on Italian data2,37 we argued that the comparison of screen detected cases with all the outside screening breast cancer cases could be biased, because survival rates of never responders might be different for reasons not related to stage, for example, socioeconomic status or different access to appropriate treatment. In this paper we performed an intention to treat analysis to adjust for the possible selection bias. The implication of our study is that stage distribution entirely explained the difference of survival observed between invited and non invited in the 5–10 years window suggesting minimal or any length bias.

5. Conclusions

There are several possible distortions in the interpretation of the benefit of survival as true mortality benefit for the target population. We have shown that pathological T, nodal status and grade at diagnosis are very good predictors of the survival curve, at least in women aged 50–64 years. The proportionality of hazards in the second 5-year period showed that the survival benefit was not lost, but the length of the follow-up is possibly still too short to give a lead time free estimate of the benefit.

In the [5–10] year time window we have estimated a 36% reduction of the hazard, which in absolute terms is a reduction of 8.2 breast cancer deaths in 1000 cases in the invited group. Applying this reduction to the 7379 invited cases (with 46,373.4 person years), the number of lives saved at 10 years is estimated to be $8.2 \times 46,373.4/1000 = 380.3$. The estimated number of avoided deaths should be considered with caution and within a range which includes the lower limit of the confidence interval of the estimate ($N = 234.2$, 22% reduction). The analysis of survival rates suggests that service screening programmes are achieving the expected results. Longer follow-up would confirm, as in previous trials, the global benefit achieved by service screening in terms of lives saved.

Conflict of interest statement

None declared.

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