

available at www.sciencedirect.comjournal homepage: www.ejconline.com

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

Eugenio Paci^{a,*}, Enzo Coviello^b, Guido Miccinesi^a, Donella Puliti^a, Laura Cortesi^c, Vincenzo De Lisi^d, Stefano Ferretti^e, Lucia Mangone^f, Vincenza Perlangeli^g, Antonio Ponti^h, Alessandra Ravaoliⁱ, Priscilla Sassoli de' Bianchi^j, Nereo Segnan^h, Fabrizio Stracci^k, Rosario Tumino^l, Maurizio Zarccone^m, Manuel Zorziⁿ, Marco Zappa^a, IMPACT Working Group^o

^aClinical and Descriptive Epidemiology Unit – CSPO – Research Institute of the Tuscany Region, via San Salvi 12, 50135, Firenze, Italy

^bEpidemiology Unit ASL BA/2, piazza V. Emanuele 14, 70054 Giovinazzo, Bari, Italy

^cModena Cancer Registry, via del Pozzo 71, 41100, Modena, Italy

^dParma Cancer Registry, via Abbeveratoia 4, 43100, Parma, Italy

^eFerrara Cancer Registry, via Fossato di Mortara 64b, 44100, Ferrara, Italy

^fReggio Emilia Cancer Registry, via Amendola 2, 42100, Reggio Emilia, Italy

^gAUSL Bologna, Via del Seminario 1, 40068, S.Lazzaro di Savena, Bologna, Italy

^hEpidemiology Unit – CPO Piemonte, via S. Francesco da Paola 31, 10123, Torino, Italy

ⁱRomagna Cancer Registry, via Carlo Forlanini 34, 47100, Forlì, Italy

^jEmilia-Romagna Region Health Department, viale Aldo Moro 21, 40127, Bologna, Italy

^kUmbria Cancer Registry, via del Giochetto, 06100, Perugia, Italy

^lCancer Registry, A.O. “Civile M.P. Arezzo”, via Dante 109, 97100, Ragusa, Italy

^mPalermo Breast Cancer Registry, Piazzale N. Leotta 2, 90127, Palermo, Italy

ⁿVenetian Tumour Registry, Istituto Oncologico Veneto, via Gattamelata 64, 35128, Padua, Italy

* Corresponding author. Tel.: +39 055 6268329; fax: +39 055 679954.

E-mail address: e.paci@cspo.it (E. Paci).

^o E. Paci, P. Falini, D. Puliti, I. Esposito, M. Zappa, E. Crocetti, Clinical and Descriptive Epidemiology Unit – CSPO - Research Institute of the Tuscany Region; Firenze. C. Naldoni, A.C. Finarelli, P. Sassoli de' Bianchi, Screening Programme - Emilia-Romagna Region Health Dept; Bologna. S. Ferretti, Ferrara Cancer Registry; Ferrara. G.P. Baraldi, Breast Cancer Screening Programme; Ferrara. M. Federico, C. Cirilli, Modena Cancer Registry; Modena. R. Negri, ASL Modena; Modena. V. De Lisi, P. Sgargi, Parma Cancer Registry; Parma. A. Traina, M. Zarccone, Dept. of Oncology ARNAS Ascoli; Palermo. A. Cattani, N. Borciani, ASL Reggio Emilia; Reggio Emilia. L. Mangone, Reggio Emilia Cancer Registry; Reggio Emilia. F. Falcini, A. Ravaoli, R. Vattiato, A. Colamartini, Romagna Cancer Registry; Forlì. M. Serafini, B. Vitali, P. Bravetti, ASL Ravenna; Ravenna. F. Desiderio, D. Canuti, C. Fabbri, ASL Rimini; Rimini. C. Imolesi, M. Palazzi, Bertozzi, ASL Cesena; Cesena. N. Collina, P. Baldazzi, M. Manfredi, V. Perlangeli, C. Petrucci, G. Saguatti, AUSL Bologna; Bologna. N. Segnan, A. Ponti, G. Del Mastro, C. Senore, A. Frigerio, S. Pitarella, CPO Piemonte; Torino. S. Patriarca, R. Zanetti, Piemonte Cancer Registry; Torino. M. Vettorazzi, M. Zorzi, Istituto Oncologico Veneto; Padova. A. Molino, A. Mercanti, Università di Verona; Verona. R. Mariotto, Azienda ULSS Verona; Verona. R. Tumino, A. Sigona, Cancer Registry and Pathology; Ragusa. G. La Perna, C. Iacono, ONCOBLA-U.O. Oncologia, Azienda Ospedaliera Ragusa; F. Stracci, F. La Rosa Registro Tumori Umbro; Perugia. M. Petrella, I. Fusco Moffa, Epidemiology Unit ASL2; Perugia. 0959-8049/\$ - see front matter © 2008 Elsevier Ltd. All rights reserved.

doi:10.1016/j.ejca.2008.02.026

ARTICLE INFO

Article history:

Received 21 December 2007

Received in revised form

16 February 2008

Accepted 22 February 2008

Available online 21 March 2008

Keywords:

Breast cancer

Service screening

Survival

ABSTRACT

12,987 invasive breast cancer cases were diagnosed in women aged 50–69 up to the year 2001 in nine Italian areas where a screening programme was active. Cases were followed up in 2005 for a total of 1921 breast cancer failures.

The 10-year survival rates were 85.3% for the invited group against 75.6% for the non-invited. A time dependent analysis was performed using 5-year intervals. Crude hazard ratios for the invited group in comparison to the not invited group were 0.52 and 0.64 respectively in the (0–5) year and [5–10] year time windows. Hazard ratio adjusted for tumour characteristics was 0.96 in the [5–10] year time window, suggesting minimal or any length bias.

Consistent with the results of randomised trials, these analyses of service screening data document a mortality reduction of 36% at 5–10 years after diagnosis.

© 2008 Elsevier Ltd. All rights reserved.

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 (GIS-MA) was established in 1990 to improve the quality of 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 trials).²⁰ Only if it were possible to correct for lead-time and length biases could we conclude that the comparison of hazard rates of a group of invited cases with a group of non-invited cases would be a good estimate of the mortality benefit.

In this paper we present the 10-year survival data of population-based breast cancer cases in the Italian areas participating in the IMPACT study, with the aim of evaluating the impact of service screening. Using more recent statistical approaches for modelling hazards, we have tried to investigate survival rates as predictors of the real effect of screening on mortality.

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-divisions. They were:

Screen-detected (SD) cases

- 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 from the screening status, through linkage with the regional mortality registry and with the list of residents.²² 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,^{23,24} 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,²⁵ 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,²⁶ 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.²⁷ 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 not-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

	Invited group					Total Invited	Non-invited	Total
	SD Prevalence	SD Incidence	Interval cases	Interval cases	Never respondent			
			< = 2 years	>2 years				
No cases	3910	1420	874	282	1828	8314	5948	14262
%	27	10	6.1	2	13	58	42	100
pT								
pTis	517 (13)	195 (14)	58 (7.6)	26 (9.2)	101 (5.5)	897 (11)	378 (6.4)	1275 (8.9)
pTmicr	88 (2.3)	32 (2.3)	11 (1.3)	1 (0.4)	34 (1.9)	166 (2.0)	77 (1.3)	243 (1.7)
pT1a	256 (6.6)	119 (8.4)	39 (4.5)	9 (3.2)	61 (3.3)	484 (5.8)	165 (2.8)	649 (4.6)
pT1b	990 (25)	365 (26)	118 (14)	53 (19)	220 (12)	1746 (21)	802 (14)	2548 (18)
pT1c	1416 (36)	514 (36)	353 (40)	100 (36)	577 (32)	2960 (36)	2108 (35)	5068 (36)
pT1 ns	6 (0.2)	1 (0.1)	3 (0.3)	1 (0.4)	7 (0.4)	18 (0.2)	16 (0.3)	34 (0.2)
pT2+	580 (15)	173 (12)	250 (29)	79 (28)	662 (36)	1744 (21)	1940 (33)	3684 (26)
Unknown	57 (1.5)	21 (1.5)	42 (4.8)	13 (4.6)	166 (9.1)	299 (3.6)	462 (7.8)	761 (5.3)
pN ^a								
pN0	2289 (68)	786 (64)	438 (54)	143 (56)	800 (46)	4456 (60)	2793 (50)	7249 (56)
pN+	866 (26)	305 (25)	311 (38)	96 (38)	670 (39)	2248 (30)	2062 (37)	4310 (33)
Unknown	238 (7.0)	134 (11)	67 (8.2)	17 (6.6)	257 (15)	713 (9.6)	715 (13)	1428 (11)
Grading ^a								
Good (I)	900 (27)	335 (27)	123 (15)	48 (19)	220 (13)	1626 (22)	707 (13)	2333 (18)
Moderate (II)	1343 (40)	497 (41)	290 (36)	73 (29)	604 (35)	2807 (38)	1864 (34)	4671 (36)
Poor (III)	609 (18)	256 (21)	250 (31)	89 (35)	503 (29)	1707 (23)	1413 (25)	3120 (24)
Unknown	541 (16)	137 (11)	153 (19)	46 (18)	400 (23)	1277 (17)	1586 (29)	2863 (22)
No invasive cases	3393	1225	816	256	1727	7417	5570	12987
Breast cancer deaths	202	66	115	36	351	770	1151	1921

a Only invasive cases.

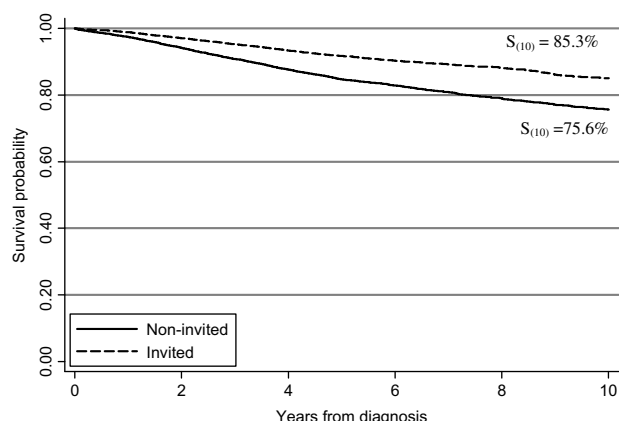


Fig. 1 – Kaplan-Meier estimates of breast cancer specific survival by invitation status.

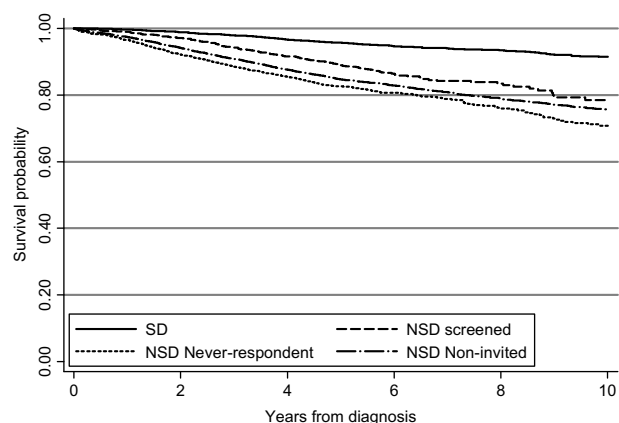


Fig. 2 – Kaplan-Meier estimates of breast cancer specific survival by detection method (Screen detected, NSD screened, NSD never responders, NSD non-invited).

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

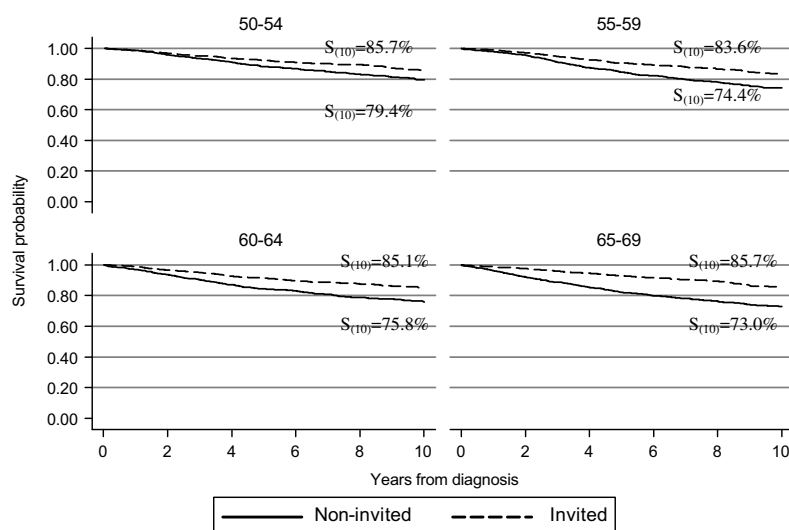


Fig. 3 – Kaplan-Meier estimates of breast cancer specific survival by invitation status and 5-year age-groups at diagnosis.

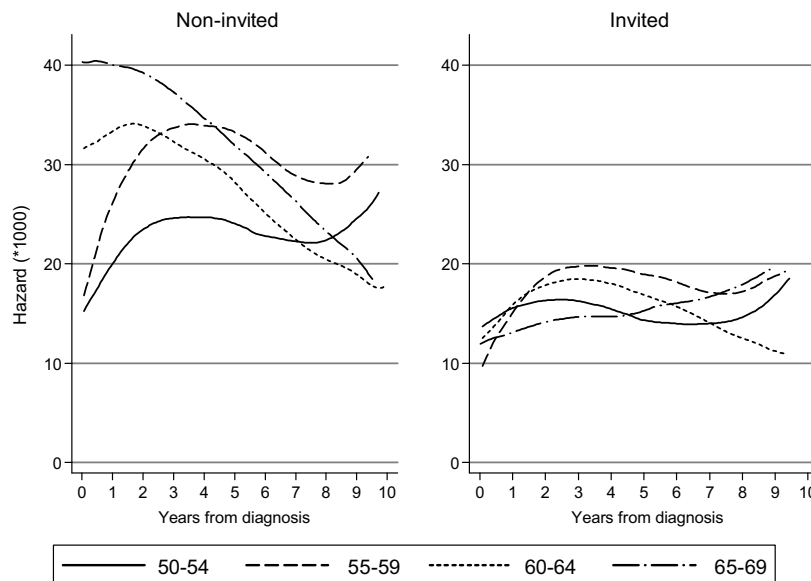


Fig. 4 – Hazard by 5-year age-group at diagnosis and invitation status.

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

Age class	Time window (years)	Hazard ratio	95% CI	Adjusted Hazard ratio	95% CI
50–54	(0 – 5)	0.65	0.52 – 0.83	1.04	0.81 – 1.33
	[5 – 10]	0.68	0.45 – 1.02	1.00	0.65 – 1.52
55–59	(0 – 5)	0.61	0.49 – 0.75	1.04	0.83 – 1.30
	[5 – 10]	0.55	0.38 – 0.78	0.88	0.60 – 1.28
60–64	(0 – 5)	0.53	0.43 – 0.65	0.87	0.70 – 1.08
	[5 – 10]	0.73	0.51 – 1.05	1.09	0.74 – 1.60
65–69	(0 – 5)	0.37	0.30 – 0.45	0.65	0.52 – 0.81
	[5 – 10]	0.63	0.44 – 0.90	0.92	0.63 – 1.35
50–69	(0 – 5)	0.52	0.47 – 0.58	0.87	0.76 – 0.99
	[5 – 10]	0.64	0.53 – 0.78	0.96	0.77 – 1.21

the invited women²⁸ and of 45% among women actually screened.²⁹

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.³⁰ 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

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 overdiagnosis concluded that the least biased estimates of overdiagnosis 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 data^{2,37} 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.

Acknowledgement

Partial contribution of a research grant from the Italian League against cancer (518, 09/26/2005) and the Ministry of Health (134/07, 02/26/2007).

REFERENCES

1. Shapiro S, Coleman EA, Broeders M, et al. Breast cancer screening programmes in 22 countries: current policies, administration and guidelines. International Breast Cancer Screening Network (IBSN) and the European Network of Pilot Projects for Breast Cancer Screening. *Int J Epidemiol* 1998;27:735–42.
2. Paci E, Ponti A, Zappa M, et al. Early diagnosis, not differential treatment, explains better survival in service screening. *Eur J Cancer* 2005;41:2728–34.
3. Perry N, Broeders M, de Wolf C, et al., editors. *European guidelines for quality assurance in breast cancer screening and diagnosis*. fourth ed. Luxembourg: Office for Official Publications of the European Commission; 2006.
4. The National Centre for Screening Monitoring: 5th Report. *Epidemiol Prev* 2007;31(Suppl 2):7–32.
5. AIRT Working Group: Italian Cancer Figures – Report 2006. Incidence, mortality and estimates. *Epidemiol Prev* 2006; 30(Suppl 2):12–25.
6. Shapiro S, Strax P, Venet L. Periodic breast cancer screening in reducing mortality from breast cancer. *JAMA* 1971;215:1777–85.
7. Tabar, Fagerberg CJ, Gad A, et al. Reduction in mortality from breast cancer after mass screening with mammography.

- Randomised trial from the Breast Cancer Screening Working Group of the Swedish National Board of Health and Welfare. *Lancet* 1985;1:829–32.
8. Andersson I, Aspegren K, Janzon L, et al. Mammographic screening and mortality from breast cancer: the Malmö mammographic screening trial. *BMJ* 1988;297:943–8.
 9. Roberts MM, Alexander FE, Anderson TJ, et al. Edinburgh trial of screening for breast cancer: mortality at seven years. *Lancet* 1990;335:241–6.
 10. Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study: 2. Breast cancer detection and death rates among women aged 50 to 59 years. *CMAJ* 1992;47:1477–88.
 11. Frisell J, Eklund G, Hellström L, Lidbrink E, Rutqvist LE, Somell A. Randomized study of mammography screening—preliminary report on mortality in the Stockholm trial. *Breast Cancer Res Treat* 1991;18:49–56.
 12. Nyström L, Rutqvist LE, Wall S, et al. Breast cancer screening with mammography: overview of Swedish randomised trials. *Lancet* 1993;341:973–8.
 13. Elmore JG, Armstrong K, Lehman CD, Fletcher SW. Screening for breast cancer. *JAMA* 2005;293:1245–56. Review.
 14. Olsen O, Gotzsche PC. Cochrane review on screening for breast cancer with mammography. *Lancet* 2001;358:1340–2.
 15. Gøtzsche PC, Nielsen M. Screening for breast cancer with mammography. *Cochrane Database Syst Rev* 2006(4):CD001877. Review.
 16. IARC handbooks of cancer prevention. *Breast cancer screening* vol. 7. Lyon: IARC; 2002.
 17. Cuzick J. Breast cancer screening—time to move forward. *Breast* 2002;11:209–10.
 18. Duffy SW, Hill C, Estève J. *Quantitative methods for the evaluation of cancer screening*. London: Arnold; 2001.
 19. Baker SG, Kramer BS, Prorok PC. Comparing breast cancer mortality rates before-and-after a change in availability of screening in different regions: extension of the paired availability design. *BMC Med Res Methodol* 2004;4:1–9.
 20. Morrison A. *Screening in chronic disease*. 2nd ed. New York: Oxford University Press; 1992.
 21. Zorzi M, Puliti D, Vettorazzi M, et al. for the IMPACT Working Group. Mastectomy rates are decreasing in the era of service screening: a population-based study in Italy (1997–2001). *British Journal of Cancer* 2006;95:1265–8.
 22. AIRTUM Working Group: Italian Cancer Figures – Report 2007. *Survival. Epidemiol Prev* 2007;30(Suppl 1):14–23.
 23. Paci E, Duffy SW, Giorgi D, Prevost TC, Rosselli del Turco M. Population-based breast cancer screening programmes: estimates of sensitivity, overdiagnosis and early prediction of the benefit. In: Duffy SW, Hill C, Esteve J, editors. *Quantitative methods for the evaluation of cancer screening*. London: Arnold; 2001. p. 127–35.
 24. Walter SD, Stitt LW. Evaluating the survival of cancer cases detected by screening. *Stat Med* 1987;6:885–900.
 25. Day NE. Overdiagnosis and breast cancer screening. *Breast Cancer Res* 2005;7:228–9.
 26. Paci E, Miccinesi G, Puliti D, et al. Estimate of overdiagnosis of breast cancer due to mammography after adjustment for lead time. A service screening study in Italy. *Breast Cancer Res* 2006;8:R68.
 27. Therneau T, Grambsch P. *Modeling survival data: Extending the Cox model*. New York: Springer; 2000.
 28. Sarkeala T, Heinavaara S, Anttila A. Organised mammography screening reduces breast cancer mortality: a cohort study from Finland. *Int J Cancer* 2008;122:614–9.
 29. Swedish Organised Service Screening Evaluation Group. Reduction in breast cancer mortality from organized service screening with mammography: 1. Further confirmation with extended data. *Cancer Epidemiol Biomarkers Prev* 2006;15:45–51.
 30. Warwick J, Tabar L, Vitak B, Duffy SW. Time-dependent effects on survival in breast carcinoma: results of 20 years of follow-up from the Swedish Two-County Study. *Cancer* 2004;100:1331–6.
 31. Giorgi D, Paci E, Zappa M, Rosselli del Turco M. Breast cancer early diagnosis experience in Florence: can a self referral policy achieve the results of service screening? *J Epidemiol Community Health* 1994;48:471–5.
 32. Biesheuvel C, Barratt A, Howard K, Houssami N, Irwig L. Effects of study methods and biases on estimates of invasive breast cancer overdiagnosis with mammography screening: a systematic review. *Lancet Oncol* 2007;8:1129–38.
 33. Zackrisson S, Andersson I, Janzon L, Manjer J, Garne JP. Rate of over-diagnosis of breast cancer 15 years after end of Malmö mammographic screening trial: follow-up study. *BMJ* 2006;332:689–92.
 34. Moss S. Overdiagnosis and overtreatment of breast cancer: overdiagnosis in randomised controlled trials of breast cancer screening. *Breast Cancer Res* 2005;7:230–4.
 35. Joensuu H, Lehtimäki T, Holli K, et al. Risk for distant recurrence of breast cancer detected by mammography screening or other methods. *JAMA* 2004;292:1064–73.
 36. Shen Y, Yang Y, Inoue LY, Munsell MF, Miller AB, Berry DA. Role of detection method in predicting breast cancer survival: analysis of randomized screening trials. *J Natl Cancer Inst* 2005;97:1195–203.
 37. Paci E, Ponti A, Crocetti E, Zappa M, Segnan N. Re: Role of detection method in predicting breast cancer survival: analysis of randomized screening trials. *J Natl Cancer Inst* 2005;97:1853–4.