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Short report

Population-based breast cancer screening in Pavia (northern Italy) in 2016-2018: key performance indicators and sensitivity estimate

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Abstract. *Background and aim:* This study aims to assess the quality of the population-based breast cancer screening programme in Pavia, northern Italy, computing its key performance indicators and estimating its sensitivity for the years 2016-2018. In the entire period the number of invited individuals was 94,420 and those participating 52,877. The overall invitation coverage was 90.2% and the adjusted participation rate 62.3%. *Methods:* Invitation and examination coverage, participation rate, recall rate, detection rate and positive predictive values were computed on the basis of data provided yearly to the Italian Ministry of Health. Sensitivity was estimated identifying interval cancers in the local Cancer Registry and computed with the proportional incidence method. *Results:* In 2016-2018 the adjusted invitation coverage was 90%, and the adjusted participation rate was 62%. Recall rate was 8.4% for first screenings and 3.9% for subsequent ones. The number of screen-detected cases was 268, corresponding to a detection rate of 6.6‰ for first screenings and 4.6‰ for subsequent screenings. The number of interval cancers observed was 110 over the study period; the proportional incidence was 22% for the first interval year and 50% for the second interval. The overall sensitivity of the screening program was 64%. *Conclusions:* The analysis of performance indicators and sensitivity estimates for the Pavia programme indicates that the programme performance is in line with the quality standards set by the European Union and the Italian reference scientific society (GISMa). (www.actabiomedica.it)

Key words: Breast cancer, mammography screening, interval cancers, sensitivity, proportional incidence

Introduction

Breast cancer is the most commonly diagnosed cancer in women in Italy, representing 29% of all malignant tumours. In the first half of 2020, breast cancer was the leading cause of cancer deaths in women, with 6,460 deaths, representing 0.9% increase compared to 2015-2019 (1).

Mammographic screening is a crucial part of essential care in Italy, introduced by the Decree of the President of the Council of Ministers on November 29, 2001, and offered free of charge to all women. The aim of mammography screening is to allow early detection and reduce breast cancer mortality. Organized screening programs in the Lombardy region were initiated in the early 2000s, with the Pavia program enrolling the first cases in 2006.

The National Screening Observatory routinely gathers screening indicators to ensure that the program's effectiveness is consistently monitored. Mortality rates

stemming from late-stage breast cancer diagnosis are typically utilized to assess the impact of breast cancer screening, and sensitivity can serve as a reliable proxy to track program performance over time (2,3).

In clinical settings, the sensitivity of a test is usually measured by comparison to a gold standard. This is rarely possible in a screening setting because the test aims to detect a lesion in the preclinical detectable phase, and only those with suspicious initial screening findings will receive further testing. Therefore, sensitivity can be estimated by collecting interval cancers, which are symptomatic cancers diagnosed after an examination with a negative result and before the subsequent scheduled examination. Interval cancer rates can be a powerful indicator of the quality of early detection (4). The most accredited method to date for estimating sensitivity is the calculation of the proportional incidence, which relates the observed interval cancers to the total number of cancers expected in the absence of screening. From this value, the sensitivity of the screening program can be calculated as the complementary to one of the proportional incidence. The collection and analysis of interval cancers have been the goal of local health protection agencies in the Lombardy region since 2012, and in 2020, a standardized analysis method was proposed for the entire region (5). This study aims to present the sensitivity estimate for the Pavia screening program using this method, along with key performance indicators for the 2016-2018 period.

Methods

Pavia breast cancer screening programme setting

In northern Italy, the province of Pavia has a population of almost 76,600, of which approximately 39,000 women are the intended beneficiaries of mammographic screening. The target population for screening consisted of females aged 50 to 69 in 2016-2017, but in 2018, the program was broadened to cover women aged 50 to 74, with an option for spontaneous enrollment for those aged 45 to 49.

The mammography screening programme in Pavia is managed by the Pavia Health Protection Agency (ATS). The ATS screening centre identifies eligible individuals from the resident population registered in the regional registry. The target population is the same as the eligible population, with the exception of those who are excluded due to criteria such as having had a recent mammography (temporary suspension) or undergoing breast tumour therapy (permanent suspension). Eligible women receive a letter of invitation that includes information about the screening programme and details of the appointment for the exam. Women who accept the invitation undergo a mammogram in two projections, and each image is independently reviewed by two radiologists. In the case of suspicious or positive results, the woman is referred for further diagnostic examinations. Women diagnosed with breast cancer are referred to one of the two breast units present in the ATS area. Women aged 50 to 74 are called back for the next mammogram after two years, while women aged 45 to 49 after one year (implementation of one year recall ongoing from 2022).

Key performance indicators computation

We have computed the following indicators for women aged 50 to 69, on the basis of data provided yearly to the Health Ministry through the National Screening Observatory and following the official definitions (6):

- adjusted invitation coverage: percentage of women invited to screening during the analysed period, compared to the target population, excluding undelivered invitations and women with specific exclusion criteria;
- examination coverage: percentage of women who performed the test compared to the target population, excluding women with specific exclusion criteria;
- adjusted participation in the screening programme (PR): percentage of invited women who performed the test within 6 months from the invitation, excluding undelivered invitations and women with recent mammography (<12 months);
- recall rate (RR): the number of women recalled for further assessments as a proportion of all women with a screening examination;

- detection rate (DR): the number of all malignant cancers detected every 1,000 screened women;
- positive predictive value (PPV): the ratio of lesions that are truly positive to those that test positive.

Sensitivity estimate

Firstly, we selected the cohort of individuals who underwent the 1st level screening test between 1st January 2016 and 31st December 2018 from the screening database. We collected records of negative results from 1st level screening with recalls one or two years later, as well as records of positive results from 1st level screening with negative results at the 2nd level. We then linked this data with the Cancer Registry to identify any breast cancers that occurred in the next screening round. Each person's record included the necessary information to define the incidence date according to the Italian Association of Cancer Registries guidelines. We excluded redundant records for the same mammography.

After identifying the cohort of screened patients with a negative and complete screening episode, we computed the person-time of follow-up for this group. Each individual in the negative cohort contributed to the person-time within the period between the date of the screening test and the occurrence of one of the following events: breast cancer diagnosis, death, emigration, subsequent screening test, or 24 months from the date of the 1st screening test.

We used the breast cancer incidence rate in the absence of screening provided by Lombardy Cancer Registries as the baseline for expected breast cancer incidence. The 95% confidence intervals were calculated using both the normal distribution and the exact Poisson distribution. We performed the data analysis using the STATA statistical package (Stata Statistical Software: Release 17, College Station, TX, USA).

Results

Table 1 presents the key performance indicators of the screening programme, for women aged 50-69 in

Table 1. Pavia breast cancer screening programme key performance indicators, 2016-2018, 50-69 years old.

	2016	2017	2018	Overall
Target population (n)	38,123	38,597	38,974	115,694
N. of invited subjects	30,974	32,642	30,804	94,420
Adjusted Invitation Coverage (%)	90.6	90.9	89.1	90.2
Examination coverage (%)	41.3	50.1	45.7	45.7
N. of screened women	15,734	19,335	17,808	52,877
Adjusted participation rate (%)	60.0	65.3	61.7	62.3
Adherence to assessment (%)	99.2	98.5	91.4	96.4
Recall rate (%)				
First screening	8.6	10.1	6.4	8.4
Subsequent	4.9	3.7	3.2	3.9
N. of screen-detected cancers	71	92	105	268
Detection rate (‰)				
First screening	5.5	7.1	7.2	6.6
Subsequent	4.2	4.1	5.6	4.6
Positive predictive value (%)				
First screening	6.4	7.2	12.9	8.8
Subsequent	8.5	11.2	19.0	12.9

order to ensure comparability with national data and standards. The invitation coverage and participation rate remained stable over the three-year period, corresponding to 90% and 45.7%, respectively. The adjusted participation rate for the entire period was 62.3%. The recall rate for first and subsequent screenings was 8.4% and 3.9%, respectively, with a high adherence to assessment of 96.4%. The number of cancers detected by screening sums up to a total of 268 cases identified. The overall DR for first and subsequent screenings was 6.6‰ and 4.6‰, respectively. The PPV was 8.8% for first screenings and 12.9% for subsequent screenings.

In this period, 110 cases of breast cancer were identified in the two years following each round of screening with a negative result: 34 in the first year and 76 in the second year. In table 2 are shown, separately by interval year (1st and 2nd year), the estimate of the proportional incidence of breast interval cancers, by five-year age classes, for the whole study period. Proportional incidence for the first interval year was 0.22, ranging from 0 (70-74 age group) to 3.29 (45-49 age group). Instead, the proportional incidence for the second interval year was 0.50, ranging from 0 (45-49 age group) to 0.84 (70-74 age group). The overall sensitivity of the programme was 64%, with 95% confidence interval ranging between 59.0% and 68.4% (data not shown).

Discussion

The analysis of performance indicators and sensitivity estimates for the Pavia breast screening programme indicates that the programme performance is in line with the standards set by the European Union and/or the Italian reference scientific society (GISMa). In Italy, between 2016 and 2018, indicators of organised mammographic screening showed an increase in invitation coverage and examination coverage, with a significant stabilisation of the participation rate (7). For the Pavia programme the percentage of invited women is higher than the national average but slightly lower with respect to the one of Northern Italy. The invitation coverage then can be considered acceptable, but it needs to be improved up to 100% in order to guarantee a maximum level of effectiveness and equity. The PR is essential to obtain an impact on cancer-specific mortality, and European standards for PR consider 70% and 75% as acceptable and desirable levels of participation, respectively. The same standards according to GISMa are set at 60% and 75% (8). In the 2016-2018 period, PR for organised mammographic screening in Italy was consistently below acceptable levels, while in Pavia, it was close to the standard for the entire period. However, the examination coverage in Pavia suffered a decline of almost 5% in 2018 compared to the previous year; this is probably an artefact due to unbalances in the number of invited women across years. During the same period, a significant RR increase and a slight PPV reduction were recorded in the national scenario. In contrast, in Pavia, RR decreased, and PPV slightly increased for subsequent screenings. Analysing the RR (a screening specificity indicator), at the first screening, the acceptability threshold (<7%) is always exceeded. Results are better for RR at subsequent screening, as it was consistently below the threshold of acceptability

Table 2. Interval cancers proportional incidence, per age groups and interval year.

	First interval year						Second interval year					
Age group	Total n. of women with negative screening	Follow-up person-time	Incidence rate (by 100,000)	N. of expected breast cancers	Interval cancers	Proportional incidence	Total n. of women with negative screening	Follow-up person-time	Incidence rate (by 100,000)	N. of expected breast cancers	Interval cancers	Proportional incidence
45-49	413	410.6	222.4	0.91	3	3.29	172	169.0	222.4	0.38	0	0.00
50-54	16321	16283.9	249.0	40.55	11	0.27	12,814	12,483.9	249.0	31.09	17	0.55
55-59	13767	13739.9	238.6	32.78	6	0.18	14,829	14,663.8	238.6	34.99	13	0.37
60-64	12171	12157.1	273.8	33.29	5	0.15	12,494	12,357.4	273.8	33.83	14	0.41
65-69	11533	11511.7	287.6	33.11	9	0.27	11,495	11,362.7	287.6	32.68	16	0.49
70-74	3990	3981.5	311.0	12.38	0	0.00	6,226	6,146.0	311.0	19.11	16	0.84
Total	**58,195**	**58,084.7**		**153.02**	**34**	**0.22**	**58,030**	**57,182.8**		**152.08**	**76**	**0.50**

(<5%) and had a constant trend over time. The DR of malignant tumors was higher in the first screening than in subsequent screenings and in older age groups due to a higher prevalence of the disease in this population. As expected, PPV values were lower and less stable during the first screening than during subsequent ones. Finally, the global sensitivity for the Pavia program for the period of 2016-2018 was estimated to be 64% (95% Cis: 59%; 68.4%). The European guidelines have set the gold standards for the proportional incidence at <30% for the first year after the screening episode, <50% for the second year, and <40% for the two-year period (that corresponds to 60% sensitivity) (9). The overall programme sensitivity, then, meets the European standard.

The effectiveness of mammographic screening is closely related to the reading performance of radiologists, the quality of images and the overall organisational quality of breast cancer screening programs. If the aim of screening programs is the early detection of malignant lesions (high sensitivity), this should ideally be accompanied by an acceptable RR and a low frequency of biopsies (high specificity), also to limit anxiety and stress in the involved women. Thus, good RR, DR and PPV values indicate good quality of the programme and a positive impact on breast cancer mortality. Moreover, high RR highlights performance worsening with risks of organisational unsustainability of the programmes. Several reasons could explain the increase in RR. First, the lack of previous mammographic images could explain high RR, especially at the first screening test, when women are also younger and with more dense breasts than older women. Second, inadequate training for new health professionals involved in breast cancer screening programs. Screening radiologists require dedicated training and should ensure a minimum annual volume of readings (between 3,500 and 11,000 mammograms/year, as indicated by the European Commission Initiative on Breast Cancer, ECIBC) to achieve and maintain high reading performances.

Taking our results into account within a broader context, a recent study conducted by Bucchi et al. (2018) in Emilia Romagna, Italy, which assessed the incidence of interval breast cancers diagnosed in a cohort of 650,000 negative mammograms, found an incidence of interval breast tumors of 0.45 (45%) for the second year after a negative screening (10). For territorial comparison, a study conducted by Local Health Authority (ASL) of Milan 1 reported that the proportional observed/expected interval cancer rate in the first or second year of screening interval was 26% or 67%, respectively (11). In the international scenario, Taylor et al. (12,13) reviewed estimates of proportional incidence in the first year of the screening interval by comparing international data published since 1975, including results from randomised trials and routine screening programs in Australia, Canada, Italy, the Netherlands, Scandinavia, the United Kingdom, and the United States (Health Insurance Plan study). They found wide variability, with an overall point estimate of the proportional incidence of 18.5% from all randomized trials and 27.3% from service screening programs, corresponding to an episode sensitivity estimate of 91.5% for the randomized trials and 72.7% for service screening. A pooled analysis in the service screening centers of six European countries reported significant variation in screening sensitivity and performance, with a proportional incidence of 46% (episode sensitivity, 54%) in the 24 months after screening (14). The European standards were 30% and 50% for the proportional incidence at the prevalent screen and at subsequent screenings, respectively, corresponding to recommended episode sensitivities of 70% and 50%. Therefore, the values of proportional incidence at the first and second interval years observed in Pavia are consistent with the references mentioned above and are comparable to those reported by other programmes at national and international level.

Our study has some limitations. First, our study is observational and it shares the limitations common to all the routine screening studies (e.g. self-selection of the sample, etc.). Secondly, our cohort sample size is relatively small, and being the event of interval cancer rare the precision of the sensitivity estimate is not that high. Finally, as recently pointed out by Chubak et al. (15), interval cancer rate cannot be considered a pure measure of test sensitivity. A strong point of this study is that it is the first one carried out in the Pavia area and in the Lombardy region since 2005, as well as with a standardized methodology. Future perspectives

are to expand the time window to have a more stable sensitivity estimate. Furthermore, it would be useful comparing interval cancers with screen-detected cancers in terms of cancer molecular and biological characteristics and to assess the 5-year survival in both cohorts.

In conclusion, our study suggests that the mammographic screening programme in Pavia is effective, as its key performance indicators and sensitivity comply with European guideline recommendations. The parameters assessed in this work were recently proposed as candidate breast cancer screening programmes performance indicators by the European Commission Initiative on Breast Cancer (ECIBC) and they well represent the different quality process domains in member states programmes (16).

Conflicts of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Ethic Committee: Due to the retrospective, observational and anonymous nature of the study ethical committee approval was not deemed necessary.

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References

1. AIOM. I numeri del cancro in Italia 2022. 2022 Dec. [Internet] Available from: https://www.aiom.it/wp-content/uploads/2022/12/2022_AIOM_NDC-web.pdf
2. Zorzi M, Guzzinati S, Puliti D, Paci E. A simple method to estimate the episode and programme sensitivity of breast cancer screening programmes. Journal of Medical Screening. 2010;17(3):132-138. doi:10.1258/jms.2010.009060
3. Giudici F, Bortul M, Clagnan E, et al. Effetti precoci dell'adesione al programma di screening mammografico della Regione Friuli Venezia Giulia sull'incidenza del cancro della mammella in stadio avanzato: uno studio di coorte [Early effects of attendance to the Friuli Venezia Giulia (Northern Italy) mammography screening programme on the incidence of advanced-stage breast cancer: a cohort study]. Epidemiol Prev. 2020 Mar-Jun;44(2-3):145-153. [Italian]. doi: 10.19191/EP20.2-3.P145.037.
4. Bennett RL, Sellars SJ, Moss SM. Interval cancers in the NHS breast cancer screening programme in England, Wales and Northern Ireland. Br J Cancer. 2011 Feb 15;104(4):571- 7. doi: 10.1038/bjc.2011.3.
5. Coppola L, Schivardi MR, Deandrea S. Analisi e monitoraggio dei cancri di intervallo nei programmi di screening oncologici organizzati. Indirizzi metodologici. 2020, Jun. [Italian].
6. Ciatto S, Naldoni C, Ponti A, et al.; Gruppo di Studio Italiano per lo Screening Mammografico. I carcinomi di intervallo quali indicatori di performance di un programma di screening [Interval cancers as indicators of performance in screening programmes]. Epidemiol Prev. 2008 Mar-Apr;32(2):93-8. [Italian].
7. Battisti F, Mantellini P, Falini P, et al. Key performance indicators of breast cancer screening programmes in Italy, 2011-2019. Ann Ist Super Sanita. 2022 Oct-Dec;58(4):244-253. doi: 10.4415/ANN_22_04_04.
8. Giordano L, Giorgi D, Frigerio A, et al.; Gruppo Italiano per lo Screening Mammografico. Indicatori e standard per la valutazione di processo dei programmi di screening del cancro della mammella [Process indicators and standards for the evaluation of breast cancer screening programmes]. Epidemiol Prev. 2006 Mar-Apr;30(2 Suppl 1):5-9, 11-47. [Italian].
9. European Commission. European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis. 4th edition. In Perry N., Broeders M., de Wolf C. i wsp. (red.): Office for Official Publications of the European Communities, Luxembourg 2006.
10. Bucchi L, Ravaioli A, Foca F, Colamartini A, Falcini F, Naldoni C. Incidence of interval breast cancers after 650,000 negative mammographics in 13 Italian health districts. Journal of Medical Screening. 2008;15(1):30-35. doi:10.1258/jms.2008.007016
11. Burani R, Caimi F, Maggioni C, et al. Quality assessment of the mammographic screening programme in the Azienda Sanitaria locale Provincia Milano 1 -- analysis of interval cancers and discussion of possible causes of diagnostic error. Radiol Med. 2005 Mar;109(3):260-7. [English, Italian].
12. Taylor R, Supramaniam R, Rickard M, Estoesta J, Moreira C. Interval breast cancers in New South Wales, Australia, and comparisons with trials and other mammographic screening programmes. Journal of Medical Screening. 2002;9(1):20-25. doi:10.1136/jms.9.1.20
13. Taylor R, Page A, Bampton D, Estoesta J, Rickard M. Age-specific interval breast cancers in New South Wales and meta-analysis of studies of women aged 40-49 years. J Med Screen. 2004;11(4):199-206. doi: 10.1258/0969141042467403.
14. Törnberg S, Kemetli L, Ascunce N, et al. A pooled analysis of interval cancer rates in six European countries. Eur J Cancer Prev. 2010 Mar;19(2):87-93. doi: 10.1097/CEJ.0b013e32833548ed.

15. Chubak J, Burnett-Hartman AN, Barlow WE, et al. Estimating Cancer Screening Sensitivity and Specificity Using Healthcare Utilization Data: Defining the Accuracy Assessment Interval. Cancer Epidemiol Biomarkers Prev. 2022;31:1517-20. doi: 10.1158/1055-9965.EPI-22-0232.
16. Muratov S, Canelo-Aybar C, Tarride JE, et al. Monitoring and evaluation of breast cancer screening programmes: selecting candidate performance indicators. BMC Cancer. 2020;20:795. doi: 10.1186/s12885-020-07289-z

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