Original Article

Decreasing Incidence of Late-Stage Breast Cancer After the Introduction of Organized Mammography Screening in Italy

Flavia Foca, BStat[1]; Silvia Mancini, BStat[1]; Lauro Bucchi, MD[1]; Donella Puliti, PhD[2]; Marco Zappa, MD[2]; Carlo Naldoni, MD[3]; Fabio Falcini, MD[1]; Maria L. Gambino, PhD[4]; Silvano Piffer, MD[5]; Maria E. Sanoja Gonzalez, PhD[6]; Fabrizio Stracci, MD, PhD[7]; Manuel Zorzi, MD[8]; Eugenio Paci, MD[2]; and the IMPACT Working Group

BACKGROUND: After the introduction of a mammography screening program, the incidence of late-stage breast cancer is expected to decrease. The objective of the current study was to evaluate variations in the total incidence of breast cancer and in the incidence of breast cancers with a pathologic tumor (pT) classification of pT2 through pT4 after the introduction of mammography screening in 6 Italian administrative regions. **METHODS:** The study area included 700 municipalities, with a total population of 692,824 women ages 55 to 74 years, that were targeted by organized mammography screening between 1991 and 2005. The year screening started at the municipal level (year 1) was identified. The years of screening were numbered from 1 to 8. The ratio of the observed 2-year, age-standardized (Europe) incidence rate to the expected rate (the incidence rate ratio [IRR]) was calculated. Expected rates were estimated assuming that the incidence of breast cancer was stable and was equivalent to that in the last 3 years before year 1. **RESULTS:** The study was based on a total of 14,447 incident breast cancers, including 4036 pT2 through pT4 breast cancers. The total IRR was 1.35 (95% confidence interval, 1.03-1.41) in years 1 and 2, 1.16 (95% confidence interval, 1.10-1.21) in years 3 and 4, 1.14 (95% confidence interval, 1.08-1.20) in years 5 and 6, and 1.14 (95% confidence interval, 1.08-1.21) in years 7 and 8. The IRR for pT2 through pT4 breast cancers was 0.97 (95% confidence interval, 0.90-1.04) in years 1 and 2, 0.81 (95% confidence interval, 0.75-0.88) in years 3 and 4, 0.79 (95% confidence interval, 0.73-0.87) in years 5 and 6, and 0.71 (95% confidence interval, 0.64-0.79) in years 7 and 8. **CONCLUSIONS:** A significant and stable decrease in the incidence of late-stage breast cancer was observed from the third year of screening onward, when the IRR varied between 0.81 and 0.71. ***Cancer*** **2013;119:2022-8.** © *2013 American Cancer Society.*

KEYWORDS: breast cancer, incidence, mammography, screening, tumor stage.

Corresponding author: Lauro Bucchi, MD, Romagna Cancer Registry, IRST, 47014, Meldola, Forlì, Italy; l.bucchi@irst.emr.it

[1]Romagna Cancer Registry, Romagna Cancer Institute, Meldola, Forli, Italy; [2]Clinical and Descriptive Epidemiology Unit, Cancer Prevention and Research Institute, Florence, Italy; [3]Department of Health, Emilia-Romagna Region, Bologna, Italy; [4]Epidemiology Unit, Varese Health Care District, Varese, Italy; [5]Epidemiology Unit and Cancer Registry, Trento, Italy; [6]Epidemiology Unit and Cancer Registry, Sondrio Health Care District, Sondrio, Italy; [7]Department of Medical-Surgical Specialties and Public Health, University of Perugia, Perugia, Italy; [8]Veneto Cancer Registry, Veneto Oncology Institute, Institute for Cancer Research and Treatment, Padova, Italy

Stefano Ciatto died on May 4, 2012. He contributed greatly to the development of screening programs in Italy. This paper is dedicated to his memory.

The membership of the IMPACT Working Group is as follows: E. Paci, D. Puliti, M. Zappa, G. Miccinesi, P. Falini, E. Crocetti, and G. Manneschi (Cancer Prevention and Research Institute, Florence); N. Segnan, A. Ponti, L. Giordano, C. Senore, A. Frigerio, S. Pitarella, and M. P. Mano (Piemonte Center for Cancer Epidemiology and Prevention, San Giovanni Battista University Hospital Center, Torino); R. Zanetti, S. Patriarca, and S. Rosso (Piemonte Tumor Registry, Piemonte Center for Cancer Epidemiology and Prevention, San Giovanni Battista University Hospital Center, Torino); A. Sapino (San Giovanni Battista University Hospital Center, Torino); S. Pisani, M. L. Gambino, and L. Balconi (Epidemiological Observatory, Local Health Authority, Varese); P. Contiero, G. Tagliabue, and L. Preto (Tumor Registry and Environmental Epidemiology, Institute for Cancer Research and Treatment, National Tumor Institute, Milano); R. Tessandori, M. L. Annulli, S. Maspero, E. Moroni, and M. E. Sanoja Gonzalez (Epidemiological Observatory, Local Health Authority, Sondrio); S. Piffer, S. Franchini, M. A. Gentilini, M. Cappelletti, and L. Battisti (Epidemiological Observatory, Provincial Healthcare Trust, Trento); M. Pellegrini (Screening Mammography, Provincial Healthcare Trust, Trento); E. Galligioni (Medical Oncology Unit, Santa Chiara Hospital, Trento); M. Zorzi, S. Baracco, C. Fedato, S. Guzzinati, A. R. Fiore, M. Baracco, A. Dal Cin, D. Monetti, A. Rosano, and S. Ciatto (Tumor Registry, Veneto Oncology Institute, Institute for Cancer Research and Treatment, Padova); A. Molino (University of Verona, Verona); F. Caumo (Local Public Health Authority 20, Verona); M. Pieno and M. Bovo (Local Public Health Authority 9, Treviso); L. Gallo and A. Stomeo (Local Public Health Authority 18, Rovigo); D. Serraino, L. Dal Maso, M. de Dottori, A. De Paoli, A. Zucchetto, O. Forgiarini, E. De Santis, and L. Zanier (Department of Epidemiology and Biostatistics, Institute for Cancer Research and Treatment, Oncology Referral Center, Aviano); C. Naldoni, A. Finarelli, and P. Sassoli (Emilia-Romagna Region, Bologna); N. Collina, C. Petrucci, and V. Perlangeli (Breast Cancer Registry, Local Public Health Unit, Bologna); A. Pasquini, P. Baldazzi, M. Manfredi, and G. Saguatti (Breast Screening, Local Public Health Unit, Bologna); S. Ferretti (Ferrara Cancer Registry, Ferrara); G. P. Baraldi and G. Benea (Breast Screening, Local Public Health Unit, Ferrara); M. Federico and C. Cirilli (Modena Cancer Registry, Modena); E. Gallo and R. Negri (Breast Screening, Local Public Health Unit, Modena); V. De Lisi, P. Sgargi, and M. Michiara (Parma Cancer Registry, Parma); G. M. Conti (Breast Screening, Local Public Health Unit, Parma); L. Mangone and N. Borciani (Reggio Emilia Cancer Registry, Reggio Emilia); C. A. Mori, A. Cattani, L. Paterlini, and C. Campari (Breast Screening, Local Public Health Unit, Reggio Emilia); F. Falcini, A. Ravaioli, and R. Vattiato (Romagna Cancer Institute, Institute for Cancer Research and Treatment, Meldola); M. Serafini, B. Vitali, and P. Bravetti (Breast Screening, Local Public Health Unit, Ravenna); D. Canuti, C. Fabbri, and G. Monticelli (Breast Screening, Local Public Health Unit, Rimini); C. Imolesi, M. Palazzi, N. Bertozzi, and M. Faedi (Breast Screening, Local Public Health Unit, Cesena); F. Stracci and F. La Rosa (Umbria Tumor Registry, Perugia); M. Petrella and I. Fusco Moffa (Epidemiology Unit, Local Health Unit 2, Perugia); M. Fusco (Campania Regional Tumor Registry, Local Health Unit NA4, Napoli); C. Maione (Maternity-Infant Service, Local Health Unit NA4, Napoli); M. Castaing, G. Benedetto, M. Fidelbo, G. Sciacchitano, E. Vasquez, S. Cordio, and S. Sciacca (University of Catania, Integrated Tumor Registry of Catania, Messina, Siracusa, and Enna); A. Traina and M. Zarcone (Department of Oncology, ARNAS Ascoli Civic Hospital, Palermo); A. Sigona and R. Tumino (Unit of Anatomic Pathology, Local Health Unit 7, Ragusa); C. Iacono and G. La Perna (Oncology Unit, Local Health Unit 7, Ragusa); A. Madeddu, M. L. Contrino, and F. Tisano (Integrated Tumor Registry of Catania, Messina, Siracusa, and Enna; Siracusa Section, Siracusa); and P. Candela and T. Scuderi (Department of Prevention, Local Public Health Unit, Trapani).

DOI: 10.1002/cncr.28014, **Received:** November 3, 2012; **Revised:** January 9, 2013; **Accepted:** January 16, 2013, **Published online** March 15, 2013 in Wiley Online Library (wileyonlinelibrary.com)

INTRODUCTION

In the Swedish Two-County trial of mammography screening, the incidence of stage II and greater breast cancer in the study group began to decrease 5 years after randomization.[1] The difference from the control group stabilized at approximately −30% in the eighth year, after which the curves of the cumulative incidence rates remained parallel to each other. These curves corresponded well to those for mortality.

These findings suggested that the decrease in the incidence of late-stage breast cancer that is observed (or expected to be observed) some years after the introduction of a mammography screening program is an early surrogate indicator of a reduction in mortality.[2] It provides evidence that early detection has interrupted the natural history of an appreciable number of preclinical cancers with a potential to progress and become lethal.

For this reason, the effect of mammography screening programs on the incidence of late-stage breast cancer in target populations has been the subject of several investigations. In general, the results have fallen short of expectations. With considerable differences in design, tumor stage grouping, duration of observation, and statistical methods, studies from Finland[3]; the United Kingdom[4]; the Netherlands[5-7]; and New South Wales, Australia[8] have associated the introduction of organized mammography screening with a decrease of approximately 10% to 20% in the incidence rate of advanced disease. A comparable number of studies from Norway[9]; southern Netherlands[10]; Switzerland[11]; Victoria, Australia[12]; Rhode Island[13]; and New Mexico[14] have demonstrated either no decrease or only a nonsignificant decrease. In this article, we report a study that was designed to assess changes in the total incidence of breast cancer and in the incidence of late-stage breast cancer after the introduction of organized mammography screening in Italy.

MATERIALS AND METHODS

Setting: The Italian Organized Mammography Screening Programs

In Italy, decisions regarding whether and when to introduce organized mammography screening rest with the governments of the administrative regions. The planning of regional screening programs is decentralized at the health care district level, and further variation in timing of implementation occurs between municipalities—the smallest level of local government. This accounts for the reality that the introduction of screening has been gradual over the last 20 years and has not yet been completed. In 2009, the proportion of Italian women ages 50 to 69 years who ever had been invited to screening was 70%.[15] Although women ages 70 to 74 years are not in the nominal target population, many of them are invited, because the lists of the target population at the local level are updated at relatively long time intervals.

The IMPACT Project

This report addresses a secondary analysis of data from the IMPACT project, a national, cancer registry-based investigation into the results of ongoing screening programs.[16-18] The 2009 update of the IMPACT database included 82,680 registered patients with breast cancer ages 40 to 79 years from 10 administrative regions which were targeted at least in part by organized mammography screening. The participating registries also provided data on the population of women in the 1306 municipalities of the study area by 1-year age group and year of registration.

In Italy, variation in the year of implementation of screening between municipalities is combined with equally wide variation in the spatial and temporal coverage of cancer registration. The time period covered by the IMPACT database was between 1988 and 2006.

Rationale and Design

Studies of trends in breast cancer incidence after the start of screening are temporal correlation studies. These are aimed at detecting a relation between 2 characteristics, such as exposure to screening and the risk of late-stage breast cancer, both of which are measured at the aggregate level rather than at the individual level.

The validity of this design is strengthened if the study population is rapidly saturated with the factor of interest. Ideally, this should take less time than that needed for the expected effect to become visible. From this point of view, public health mammography screening programs have 2 disadvantages: their target population is a dynamic one, and their full implementation takes much longer than the nominal 2 years.[4,7,8] At any point in time, there are always population subgroups, defined by women's age and residence, whose exposure time to screening is too short to have an impact on the incidence of late-stage breast cancer. This causes a dilution over time of the screening benefit, as has been the case historically for the effect of Papanicolaou smear screening on incidence and mortality rates from cervical cancer in Denmark and Norway compared with Finland and Sweden.[19]

Because of these problems, we designed the current study as follows: 1) we excluded women ages 50 to 54 years, because they had $\leq$5 years of exposure to screening; 2) we defined the year screening started at the municipality level as the first year in which a screen-detected breast

TABLE 1. The Study Area: Registries, Number of Municipalities, Years of Introduction of Organized Mammography Screening at the Municipality Level, Number of Years of Registration, Number of Incident Breast Cancers Before and After the Introduction of Organized Mammography Screening: Ages 55 to 74 Years

Registry	No. of Municipalities	Years of Screening Introduction	No. of Years of Registration				No. of Registered Breast Cancers	
			Before		After[a]			
			Min	Max	Min	Max	Before	After[a]
Firenze	8	1991-1998	1	3	6	8	325	1900
Romagna	67	1995-2000	3	3	4	8	926	3044
Modena	47	1995-2001	3	3	5	8	683	2091
Ferrara	26	1997-1999	3	3	5	7	465	1389
Parma	47	1997-2002	3	3	3	8	462	1440
Umbria	15	1998-2002	1	3	1	5	29	199
Rovigo	40	1998-2002	2	3	1	5	163	374
Bologna	50	1998-2003	1	3	1	6	214	1098
Reggio Emilia	38	1998-2003	1	3	2	7	213	735
Verona	33	1999-2002	2	3	1	4	338	769
Trento	197	2000-2003	3	3	1	4	408	607
Sondrio	75	2000-2005	3	3	1	6	158	362
Varese	57	2001-2001	3	3	1	1	618	439
Total	700	1991-2005	1	3	1	8	5002	14,447

Abbreviations: Min, minimum; Max, maximum.
[a] Values include the year of screening introduction.

cancer was registered, and we numbered the years of screening consecutively from year 1 (the year screening started) to year 8[20]; 3) we restricted the study to those municipalities in which the proportion of total incident cancers that were detected by screening (a proxy of the saturation of the target population) reached the arbitrary level of 30% within year 2, ie, the first full year of the program; 4) we assumed that the annual incidence that would be expected in the absence of screening was stable and was equivalent to that observed in the last 3 years before year 1[5,7,8]; 5) we evaluated the effect of screening from year 1 to year 8 based on the decreasing number of available municipalities; and 6) to determine whether the progressive decrease in the study population and the associated changes in its geographic composition could introduce a bias into the results, we performed a supplementary analysis of the subgroup of municipalities that had a complete 8-year period of observation.

Population and Cancer Cases

After identifying those municipalities in which screen-detected cancers accounted for $\geq$30% of the total incidence in year 2, we selected the population ages 55 to 74 years and the registered cases of invasive (including microinvasive) breast cancer. The study area included 13 registries and 700 municipalities in 6 administrative regions of central and northern Italy (Table 1). The eligible population included 692,824 women in year 1 and 300,859 women in year 8. The different time periods of registration were between 1990 and 2006. The total number of eligible cancer cases was 5002 in the years before year 1 and 14,447 in years 1 through 8.

Tumor Stage Classification

We classified the stage of disease using pathologic tumor (pT) information rather than the pathologic lymph node (pN) or pTpN classification, as suggested by others[2,6,8]. The pT information was available for a larger proportion of patients and was less prone to stage migration bias, which occurs when technologic improvements in staging over time result in certain tumors being classified to higher stages than they would have been in an earlier period.[21,22] Late-stage breast cancer was defined as pT2, pT3, and pT4. The pT status was established using the original pT classification or, if this was not available, the reported greatest dimension of the primary tumor, with cancers >20 mm classified as pT2 through pT4.

Statistical Methods

The study endpoints were the total incidence of breast cancer and the incidence of pT2 through pT4 breast cancer. A change in incidence was calculated as the ratio, with 95% confidence interval (CI), between the observed 2-year, age-standardized (Europe) incidence rate and that expected (the incidence rate ratio [IRR]).

The total and tumor stage-specific expected rates per 100,000 population were calculated using the rates registered in the last 3 years before year 1, except for a small

minority of municipalities in which only 1 or 2 years of registration were available (Table 1). Because of the study design, the population decreased with time, and the geographic basis varied. The expected incidence rates were calculated using the prescreening incidence data specifically registered in those municipalities that formed the geographic basis of the study in each year from year 1 to year 8. Incidence data from all eligible municipalities were used for the length of time that they were covered by registration.

The proportion of stage pTX cancers, which was 10% in year 1, decreased to 9% in year 2 and to $\leq$5% thereafter. To minimize the biasing effect of this decreasing trend on the trend in tumor stage-specific incidence, both the observed rate and the expected rate were adjusted by allocating a proportion of pTX cancers to the pT2 through pT4 tumor category. This proportion was estimated by stratifying pTX cancers by municipality group, patient age group, and year of screening and by applying to the number in each stratum the corresponding proportion of pT2 through pT4 cancers observed among cancers with known pT status.

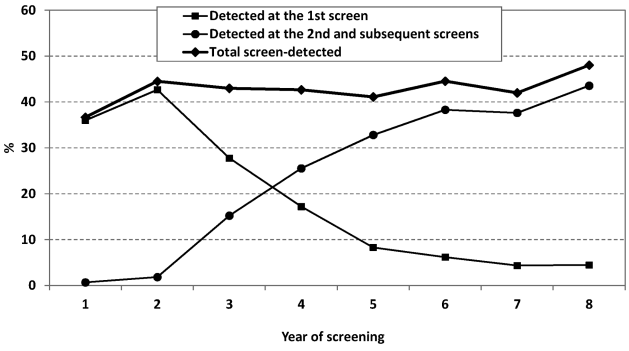

Figure 1. The proportion (%) of total incident cancers that were screen-detected is illustrated according to the year of screening (ages 55 to 74 years).

RESULTS

Figure 1 indicates that the proportion of total incident cancers detected by screening at the first screen peaked at 43% in year 2, ie, the first full year of the program. The proportion decreased thereafter and stabilized at 5% to 10% from year 5 onward. Because cancers detected on subsequent screens increased accordingly, the total proportion of screen-detected cancers remained fairly stable from year 2 onward, with values generally between 40% and 45%.

The 14,447 eligible cancers registered in year 1 to year 8 included 4036 (28%) pT2 through pT4 cancers. Table 2 provides the number of woman-years of observation, the observed and expected incidence rates of late-stage cancer and total cancers, and the point estimate with 95% CI for the IRRs according to 2-year time periods.

The plots of these IRRs are provided in Figure 2. The vertical lines in the figure indicate the 95% CIs, and the bold horizontal line is set at an IRR of 1.0 and indicates no difference between observed and expected rates. The total incidence rate rose by 35% in years 1 and 2 and stabilized thereafter at a level that was approximately 15% higher than expected.

After the introduction of screening, the incidence of late-stage breast cancer remained unchanged during years 1 and 2. A significant and stable decrease was observed from year 3 onward, when the IRR varied between 0.81 and 0.71.

In the subgroup of municipalities that had 8 years of observation, the observed incidence rate of late-stage breast cancer in the four 2-year time periods was 106.0 in years 1

TABLE 2. Number of Woman-Years of Observation, Observed and Expected Age-Standardized (Europe) Incidence Rate of Breast Cancer per 100,000 Woman-Years, and Observed-to-Expected Incidence Rate Ratios according to 2-Year Screening Period: Ages 55 to 74 Years

	Years of Screening			
Variable	1-2	3-4	5-6	7-8
Woman-years	1,385,612	1,225,745	1,061,543	718,661
Total breast cancer incidence				
Observed rate (no. of women)	368.2 (5129)	311.4 (3841)	308.6 (3275)	306.2 (2202)
Expected rate (no. of women)[a]	272.4 (3775)	269.4 (3302)	270.6 (2873)	267.9 (1925)
Incidence rate ratio [95% CI]	1.35 [1.03-1.41]	1.16 [1.10-1.21]	1.14 [1.08-1.20]	1.14 [1.08-1.21]
pT2 through pT4 breast cancer incidence				
Observed rate (no. of women)	104.0 (1499)	85.4 (1088)	83.2 (912)	72.3 (537)
Expected rate (no. of women)[a]	107.6 (1491)	105.1 (1288)	105.0 (1114)	101.7 (731)
Incidence rate ratio [95% CI]	0.97 [0.90-1.04]	0.81 [0.75-0.88]	0.79 [0.73-0.87]	0.71 [0.64-0.79]

Abbreviations: CI, confidence interval.
[a] Expected rates were calculated using the rates observed in the last 3 years before year 1 of screening and assuming a stable trend.

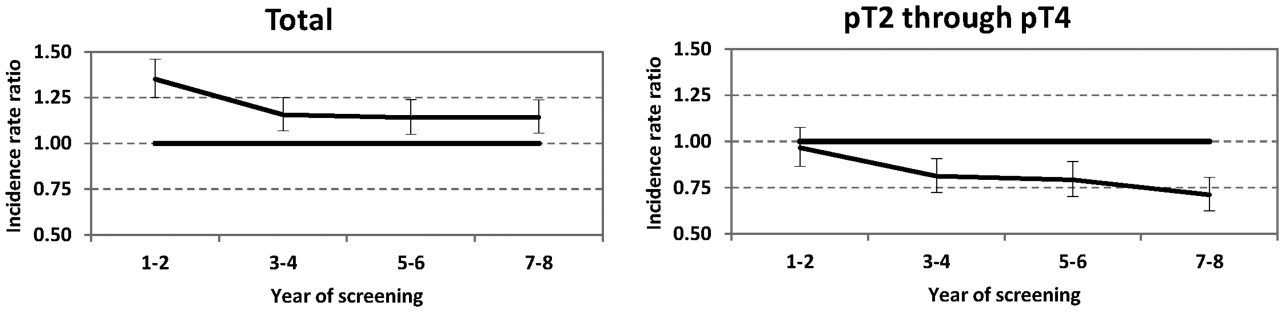

Figure 2. Ratios with 95% confidence intervals are illustrated between the observed and expected age-standardized (Europe) incidence rates of breast cancer per 100,000 women according to 2-year screening period (ages 55 to 74 years). pT indicates pathologic tumor classification.

and 2, 94.2 in years 3 and 4, 81.4 in years 5 and 6, and 71.0 in years 7 and 8. The IRR for those 4 periods was 1.07 (95% CI, 0.96-1.19), 0.95 (95% CI, 0.85-1.06), 0.82 (95% CI, 0.73-0.92), and 0.72 (95% CI, 0.63-0.81), respectively.

DISCUSSION

Study Design

In the target population of a screening program, at any point in time, there are always women for whom the duration of exposure is insufficient for the potential effect of screening on late-stage breast cancer to become apparent. The reasons are that a new birth cohort enters the target population every year and that the geographic progression of a program is gradual.

The design of this study addressed both problems. On the one hand, we excluded women ages 50 to 54 years who had $\leq$5 years of exposure. On the other hand, we synchronized the time periods of cancer registration at the municipality level[20] and excluded those municipalities in which the start-up phase of screening was relatively slow.

The combined effect of these 2 latter adjustments was that the proportion of screen-detected cancers peaked and stabilized in year 2, ie, the first full year of screening (Fig. 1). This means that we created a virtual situation in which organized screening was apparently introduced in a simultaneous manner and with great rapidity over a large geographic area. In this virtual (and ideal) setting, the real effects on incidence became appreciable.

The population decreased progressively with the year of observation, which commonly occurs in prospective studies. If the earliest screening programs, ie, those with longer follow-up, were more effective than those that were implemented later, then this would be sufficient to explain the observed changes the in IRR. In the subgroup of municipalities that had a complete 8-year period of observation, however, we observed no evidence of this greater effectiveness. The impact of screening on reducing the incidence rate of late-stage breast cancer was not greater in those municipalities with longer observation time.

Expected Incidence

Another complicated aspect of this type of study is the expected incidence.[23] Problems with long-term registration of tumor stage-specific incidence make it difficult to assess the presence of an upward or downward trend in prescreening years. In our data, the duration of cancer registration before year 1 was insufficient for most municipalities. Therefore, like many others,[5-8] we assumed that the incidence was stable for all tumor stages.

This approach could lead to either an underestimation or an overestimation of the effects of screening. In general, the opportunity of taking a pre-existing trend into account would provide a more rigorous design. However, this has one critical exception: if the trend results from a bias, then its projection would amplify the bias.[4] The advertising campaign that precedes the start of a screening program promotes higher levels of opportunistic screening. It is also possible that it results in increased awareness and prompts both an increase in the number of women responding to prevalent symptoms and a faster response to the first appearance of symptoms. All of these effects may translate into an increase in incidence and an apparent increasing trend, with an overestimation of the relative decrease observed (if any) some years later. Soon before the introduction of screening, the total incidence of breast cancer in central and northern Italy was increasing at a rate of 0.9% per year.[16] Because national survey data on mammography use have become available only recently, we cannot confirm that this finding suffered from a bias. It clearly appears, however, that our assumption of a stable incidence was conservative.

Tumor Stage Classification

Our definition of late-stage disease was based on the pT information alone because of its almost complete

availability[2] and because the pN information is prone to stage migration bias. In the United States[21] and Europe,[22] many studies covering the years between the mid-1990s and the mid-2000s, a period encompassed by our own study, have associated the introduction of sentinel lymph node biopsy with a substantial increase in the incidence of axillary lymph node micrometastases at the population level. This shift has been caused by an increasingly thorough pathologic examination of lymph nodes because of the use of serial sectioning and immunohistochemistry. Such a time trend definitely contraindicates the use of the pN information for a study of incidence trend of late-stage breast cancer over the last 20 years.

Interpretation of Results

Between the third and eighth years of organized screening, the incidence of late-stage breast cancer was 20% to 30% lower than in the last 3 years before the start of local programs. The observational nature of the study, however, does not allow us to make causal inferences. We only documented a temporal correlation between statistical aggregates. This means that intervening factors, such as increasing use of mammography outside the screening setting, may help to explain our results.

Conversely, our results are consistent with many specific data from the same screening programs. These data include a participation rate of 65%,[15] a proportional incidence of interval breast cancer well within the recommended standards,[24] a 24% decrease in incidence of total mastectomy,[17] and the results from a case-control study reporting a 25% lower breast cancer mortality among invited women versus not-yet-invited women.[18] This latter finding strongly suggests that early detection by mammography has reduced the incidence of a highly lethal condition like late-stage breast cancer.

Comparison With the Literature

In addition to the results described above, the temporal pattern of incidence of late-stage breast cancer in the current study had considerable similarities to the pattern reported in the Swedish Two-County trial.[1] In that study, the incidence of stage II or greater cancers began to decrease 5 years after randomization, and the difference between the study group and the control group stabilized at approximately −30% in year 8. However, it is important to note that women ages 50 to 74 years (74% of the study group) were invited to screening every 33 months; in other words, they had their first mammogram over a 33-month period, which was an average of 16.5 months after randomization. If this delay is taken into account, then it appears that stage II or greater breast cancers began to decrease, on average, during the third year after the first mammogram. The Two-County trial provides a good illustration that, after the introduction of screening, the incidence of late-stage breast cancer decreases fairly soon and stabilizes rapidly at a lower level (unless the sensitivity of mammography increases with time).[10]

In an observational study, the design should be able to capture this transient situation. This was not the case for many such studies, which helps explain the finding that their results were less consistent than expected.[25] In East Anglia, United Kingdom, after 6 years of screening, the incidence of stage II through IV breast cancer decreased by 7% to 19%, depending on the methods used to estimate the expected rate.[4] A Finnish study reported a 9% decrease in lymph node-positive (N+) breast cancers after 11 years.[3] Data from Limburg, the Netherlands, indicated a 10% decrease in stage II through IV cancers after 5 years[5] and an 18% decrease in T2 or greater (T2+) cancers after 9 years.[6] A Dutch national study reported a 12% decreased incidence of T2+/N+/M1 cancer after 8 years.[7] In New South Wales, Australia, the incidence of tumors that measured >30 mm in greatest dimension was 20% less than expected after 7 years.[8]

Negative studies have been reported from southern Netherlands,[10] the Swiss canton of Geneva,[11] and some Norwegian counties,[9] in which the incidence of stage II or greater breast cancer remained stable for 12 years, 16 years, and 9 years, respectively. The study from southern Netherlands covered the years from 1997 to 2008,[10] but the nationwide screening program was implemented much earlier, between 1989 and 1997.[7] In a study from Victoria, Australia, where no significant effects occurred, the observation time was as short as 4 years.[12] A study from Rhode Island reported a stable incidence of stage II through IV breast cancer between 1995 and 2001. The moderate increase in mammography rates observed between 1990 and 2001, however, could not be expected to have any measurable impact.[13]

In conclusion, we used some methodological approaches in this investigation that were designed to improve the sensitivity of a temporal correlation study toward the potential effect of organized mammography screening on the incidence of late-stage breast cancer. A significant and stable decrease was observed from the third year of screening onward, when the IRR varied between 0.81 and 0.71. This corroborates the results of observational studies that previously reported a limited but significant impact of screening on late-stage breast cancer.

FUNDING SOURCES

This work was supported by grants from the Italian League against Cancer (Decr. C.S. n. 477, October 16, 2003; Decr. C.S. n. 142, March 2, 2005), and the Italian Ministry of Health (Decr. C.S. n. 134, February 26, 2007).

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

1. Tabar L, Fagerberg G, Duffy SW, Day NE, Gad A, Grontoft O. Update of the Swedish 2-county program of mammographic screening for breast cancer. *Radiol Clin North Am*. 1992;30:187-210.
2. Day NE, Williams DRR, Khaw KT. Breast cancer screening programmes: the development of a monitoring and evaluation system. *Br J Cancer*. 1989;59:954-958.
3. Anttila A, Sarkeala T, Hakulinen T, Heinavaara S. Impacts of the Finnish service screening programme on breast cancer rates [serial online]. *BMC Public Health*. 2008;8:38.
4. McCann J, Stockton D, Day N. Breast cancer in East Anglia: the impact of the breast screening programme on stage at diagnosis. *J Med Screen*. 1998;5:42-48.
5. Schouten LJ, de Rijke JM, Schlangen JT, Verbeek AL. Evaluation of the effect of breast cancer screening by record linkage with the cancer registry, the Netherlands. *J Med Screen*. 1998;5:37-41.
6. Schouten LJ, de Rijke JM, Huveneers JA, Verbeek AL. Rising incidence of breast cancer after completion of the first prevalent round of the breast cancer screening programme. *J Med Screen*. 2002;9:120-124.
7. Fracheboud J, Otto SJ, van Dijck JA, Broeders MJ, Verbeek AL, de Koning HJ. Decreased rates of advanced breast cancer due to mammography screening in The Netherlands. *Br J Cancer*. 2004;91:861-867.
8. Kricker A, Farac K, Smith D, Sweeny A, McCredie M, Armstrong BK. Breast cancer in New South Wales in 1972-1995: tumor size and the impact of mammographic screening. *Int J Cancer*. 1999;81:877-880.
9. Hofvind S, Sorum R, Thoresen S. Incidence and tumor characteristics of breast cancer diagnosed before and after implementation of a population-based screening-program. *Acta Oncol*. 2008;47:225-231.
10. Nederend J, Duijm LE, Voogd AC, Groenewoud JH, Jansen FH, Louwman MW. Trends in incidence and detection of advanced breast cancer at biennial screening mammography in the Netherlands: a population based study [serial online]. *Breast Cancer Res*. 2012;14:R10.
11. Verkooijen HM, Fioretta G, Vlastos G, et al. Important increase of invasive lobular breast cancer incidence in Geneva, *Switzerland Int J Cancer*. 2003;104:778-781.
12. Harmer C, Staples M, Kavanagh AM. Evaluation of breast cancer incidence: is the increase due entirely to mammographic screening? *Cancer Causes Control*. 1999;10:333-337.
13. Coburn NG, Chung MA, Fulton J, Cady B. Decreased breast cancer tumor size, stage, and mortality in Rhode Island: an example of a well-screened population. *Cancer Control*. 2004;11:222-230.
14. Escobedo LG, Zhong Z, Key C. Breast and cervical cancer screening and disease incidence and stage in New Mexico. *Cancer Causes Control*. 2002;13:137-145.
15. Zappa M, Dardanoni G, Giorgi Rossi P, et al. The diffusion of screening programmes in Italy, year 2009. *Epidemiol Prev*. 2011;35(suppl 5):1-96.
16. 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 [serial online]. *Breast Cancer Res*. 2006;8:R68.
17. Zorzi M, Puliti D, Vettorazzi M, et al. Mastectomy rates are decreasing in the era of service screening: a population-based study in Italy (1997-2001). *Br J Cancer*. 2006;95:1265-1268.
18. Puliti D, Miccinesi G, Collina N, et al. Effectiveness of service screening: a case-control study to assess breast cancer mortality reduction. *Br J Cancer*. 2008;99:423-427.
19. Anttila A, Laara E. Cervix cancer: geographical correlations. In: Sankila R, Demaret E, Hakama M, Lynge E, Schouten LJ, Parkin DM, eds. Evaluation and Monitoring of Screening Programmes. Luxembourg: Office for Official Publications of the European Communities; 2001:77-98.
20. Jonsson H, Johansson R, Lenner P. Increased incidence of invasive breast cancer after the introduction of service screening with mammography in Sweden. *Int J Cancer*. 2005;117:842-847.
21. Layeequr Rahman R, Siegel E, Boneti C, et al. Stage migration with sentinel node biopsy in breast cancer. *Am J Surg*. 2009;197:491-496.
22. Maaskant AJ, van de Poll-Franse LV, Voogd AC, Coebergh JW, Tutein Nolthenius-Puylaert MC, Nieuwenhuijzen GA. Stage migration due to introduction of the sentinel node procedure: a population-based study. *Breast Cancer Res Treat*. 2009;113:173-179.
23. Broeders M, Nystrom L, Ascunce N, et al. Epidemiological guidelines for quality assurance in breast cancer screening. In: Perry N, Broeders M, de Wolf C, Tornberg S, Holland R, von Karsa L, eds. European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis. 4th ed. Luxembourg: Office for Official Publications of the European Communities; 2006:15-56.
24. Bucchi L, Ravaioli A, Foca F, Colamartini A, Falcini F, Naldoni C. Incidence of interval breast cancers after 650,000 negative mammographies in 13 Italian health districts. *J Med Screen*. 2008;15:30-35.
25. Autier P, Boniol M, Middleton R, et al. Advanced breast cancer incidence following population-based mammographic screening. *Ann Oncol*. 2011;22:1726-1735.