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ScienceDirect
The Breast 17 (2008) 477–483
THE BREAST
www.elsevier.com/locate/breast

Original article

# Breast screening: Axillary lymph node status of interval cancers by interval year

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Received 3 December 2007; received in revised form 3 March 2008; accepted 6 March 2008

**Abstract**

The aim of this study was to determine whether the excess risk of axillary lymph node metastases (N+) differs between interval breast cancers arising shortly after a negative mammography and those presenting later.

In a registry-based series of pT1a–pT3 breast carcinoma patients aged 50–74 years from the Italian screening programmes, the odds ratio (OR) for interval cancers ($n = 791$) versus the screen-detected (SD) cancers ($n = 1211$) having N+ was modelled using forward stepwise logistic regression analysis. The interscreening interval was divided into 1–12, 13–18, and 19–24 months.

The prevalence of N+ was 28% among SD cancers. With a prevalence of 38%, 42%, and 44%, the adjusted (demographics and N staging technique) OR of N+ for cancers diagnosed between 1–12, 13–18, and 19–24 months of interval was 1.41 (95% confidence interval 1.06–1.87), 1.74 (1.31–2.31), and 1.91 (1.43–2.54), respectively. Histologic type, tumour grade, and tumour size were entered in turn into the model. Histologic type had modest effects. With adjustment for tumour grade, the ORs decreased to 1.23 (0.92–1.65), 1.58 (1.18–2.12), and 1.73 (1.29–2.32). Adjusting for tumour size decreased the ORs to 0.95 (0.70–1.29), 1.34 (0.99–1.81), and 1.37 (1.01–1.85).

The strength of confounding by tumour size suggested that the excess risk of N+ for first-year interval cancers reflected only their higher chronological age, whereas the increased aggressiveness of second-year interval cancers was partly accounted for by intrinsic biological attributes.


*Keywords:* Breast cancer; Mammography; Screening

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doi:10.1016/j.breast.2008.03.005

## Introduction

In breast screening, the incidence of interval cancers increases with time since last negative mammography. There are investigators who have addressed the question of whether this quantitative trend is paralleled by changes in the biological profile of the disease. As yet, there is no independent evidence for this. In some studies, early-presenting interval cancers were found to be biologically aggressive and prognostically unfavourable.[1–3] More often, interval cancers have been reported to have biological and prognostic features unrelated to the year since last screen,[4–6] or have been treated as a unique population.[7,8]

In a different line of investigation, that of radiological review of interval cancers, it has been observed that the proportion of false-negative or missed cancers (that is, with a suspicious abnormality being identified on the original screening films) decreases with interval year, and that true interval cancers (that is, cancers interpreted on review to be not visible on the screening mammogram) are predominantly confined to the second and third years.[9–11] Among those studies that have evaluated the outcome of interval cancers undergoing review, some[12–14] (though not all)[4] have reported that true interval cancers have poorer survival rates than missed cancers. This provides a kind of ecological rationale for hypothesising that the time since last negative screen is positively associated with biological aggressiveness of interval-surfacing cancers.

In this paper, we report a large population-based study of the association between the time since last negative screen and the risk of lymph node metastases in interval breast cancers.

## Materials and methods

### *Setting*

The present study was a secondary analysis of data collected for the largest investigation to date into the results of regional breast screening programmes in Italy, the IMPACT Study.[15,16] This involves a collaborative partnership between 10 general cancer registries, three breast cancer registries, and 17 district screening units. In the study area, two-yearly mammography screening was gradually introduced between 1990 and 2001. The core target age is 50–69 years, but exceptions are made due to research purposes and management strategies.

Trained personnel from the screening units and cancer registries reviewed the case records of breast cancer patients registered between 1988 and 2001. A standard coding scheme was used to collect details for the following groups of data items: patient demographics; dates of screening mammography; detection mode; UICC TNM stage; histological diagnosis; surgical treatment; systemic treatment; post-treatment follow-up; and vital status. With respect to the detection mode, patients were classified into five groups: screen-detected (SD) on the first screen; SD on a subsequent screen; clinically diagnosed after a negative screen; non-responder to any invitation; and not yet invited to screening.

### *Objective and rationale*

The present study was based on the following assumptions: (1) in studies addressing the natural history of breast cancer in relation to mammography screening, lymph node status can be used as a well-accessible, good-quality summary indicator of aggressiveness of the disease;[17,18] (2) more precisely, lymph node status is the product of biological virulence and chronological age of the disease;[18,19] (3) tumour size is a proxy of chronological age;[8] (4) lymph node status is therefore the single most objective indicator of biological aggressiveness of the disease after adjustment for chronological age; (5) interval cancers are diagnosed later than the SD cancers; and (6), based on this consideration as well as on previous data,[20] interval cancers are expected to be larger in size and to have a greater risk of lymph node metastases than those picked up by screening.

The primary objective of the study was to determine whether and to what extent the excess risk of lymph node metastases for interval cancers in each interscreening interval year depends on their larger tumour size, that is, their higher chronological age. The rationale was two-fold: (1) if cancers arising shortly after previous screen are mostly accounted for by false-negative cancers, then their increased risk of lymph node involvement is expected to merely reflect their larger tumour size; and (2) conversely, if cancers diagnosed later are mostly true interval cancers, it is conceivable that their excess risk of lymph node involvement is only partially explained by their larger tumour size and, thus, reflects a greater biological aggressiveness.

### *Preliminary eligibility criteria*

At the time of the present analysis, there were 41,370 patients recorded in the IMPACT database. As a preliminary approach, we selected those cancers ($n = 6154$) that met the following requirements: detection by screening mammography (SD) or as an interval cancer (within 3 years of a negative mammography); patient age 50–79 years at registration; surgery as primary treatment; ICD-O histological code other than phyllodes tumour, sarcoma, lymphoma, and leukaemia; UICC stage pT 1a–3; tumour size $\geq$2 mm; number of negative axillary lymph nodes dissected $\geq$6 (no minimum requirement for positive lymph nodes and sentinel lymph node biopsy); and no distant metastases.

### *Selection of SD cancers*

Previous studies of changes in prognostic factors of breast cancer brought about by screening have removed from comparisons the length bias that may arise from contamination of SD cancers with prevalent, slow-growing cancers.[20] In a service screening programme such as that underlying the IMPACT Study data, a problem of length bias may also be

introduced by including those cancers detected on incidence screens with irregular participation. The reason is that the prevalence of cancers with low growth fraction is gradually restored at the initial level as the length of the interscreening interval increases.

In the present study, the length bias was removed by eliminating those cancers detected by a prevalence mammography ($n = 3754$) plus those detected by a repeat mammography more than 3 years after previous screen ($n = 186$), with this interval being calculated to the date of registration, that is, of first pathology report or first hospital admission.

*Selection and time categorisation of interval cancers*

There are known difficulties in differentiating SD cancers from interval cancers diagnosed around and after the completion of the 24-month interscreening interval.[21] A major source of bias for their separation is that cancer detection by rescreening acts as a competing risk for the surfacing of interval cancers. Those potential interval cancers picked up by repeat mammographies may selectively alter the biological composition of interval cancers actually observed as well as their risk of lymph node metastases.

After the exclusions described in the two paragraphs above, there remained 2214 cases. Based on their temporal distribution (Table 1), we approached the problem of rescreening as follows: (1) the interscreening interval was categorised into 1–12, 13–18, and 19–24 months; (2) the pool of interval cancers diagnosed between 1–12 and 13–18 months was assumed to be virtually unchanged by the negligible frequency of concurrent SD cancers; (3) for interval cancers observed in the last six months of the nominal two-year interval, the potential selection bias caused by rescreening was considered stronger but still acceptable since most cancers detected by screening in that time period, with an average lead time of about two years,[22] would have clinically arisen later; and (4) due to the overwhelming frequency of concurrent SD cancers, the third-year interval cancers ($n = 212$) were excluded from the study. The strength of the potential selective effects on these cases (entirely accounted for by screening cessation at 70 years of age, voluntary discontinuation, and delay in invitation) suggested that extrapolation of their characteristics to a true three-yearly screening setting was unwarranted.

Table 1
Screen-detected cancers and interval cancers by time interval since last negative mammography

| | Time interval (months)[a] | | | | | | Total |
|---|---|---|---|---|---|---|---|
| | 1–6 | 7–12 | 13–18 | 19–24 | 25–30 | 31–36 | |
| Screen-detected cancers | | | | | | | |
| Number | 0 | 1 | 7 | 143 | 811 | 249 | 1211 |
| % of total cancers | 0.0 | 0.5 | 2.6 | 36.1 | 85.7 | 76.4 | 54.7 |
| Interval cancers | 72 | 201 | 265 | 253 | 135 | 77 | 1003 |
| Total | 72 | 202 | 272 | 396 | 946 | 326 | 2214 |

[a] The interval was calculated between the date of last negative mammography and the date of cancer registration (that is, first pathology report or first hospital admission).

*Data analysis*

After all of the above exclusions were done, there remained a total of 2002 cancers available for analysis, including 1211 SD cancers and 791 interval cancers. The year of registration varied between 1992 and 2001. The patient age range was 50–74 years.

Before analysis, the potential magnitude of the sampling bias resulting from eligibility and selection criteria was assessed. The number of cancers excluded due to missing information (tumour size, nodal status, or dates of mammography) but in line with the other requirements (patient age, primary treatment, histologic type, tumour stage, and detection mode) was 649. This was compatible with a maximum potential number of 2651 cancers eligible for analysis. The subset studied ($n = 2002$) accounted for 75% of this theoretical population. Based on the partial data available, the cancers excluded were smaller in size and more differentiated. Their distribution by detection mode was non-significantly different from that of cases selected for analysis.

As expected from a previous study including part of this case series,[18] a check for the frequency distribution of tumour size showed a dominant tendency for this variable to be expressed as discrete multiples of 5 mm (data not shown). This made it impossible both to use tumour size as a continuous variable and to chose cut-offs at multiples of 5 or 10 mm as in the TNM convention. Therefore, tumour size was categorised as 2–7, 8–12, 13–17, 18–22, 23–27, and $\geq$28 mm.

Univariate associations were tested for significance ($p < 0.05$) using the Mann–Whitney test, the Kruskal–Wallis test, and the Pearson $\chi^2$ test. The odds ratio (OR) for each time-specific subset of interval cancers versus the SD cancers having positive lymph nodes was modelled as a function of potential explanatory variables using forward stepwise logistic regression analysis. The following covariates were considered: registry or health area of residence ($n = 11$); time period of diagnosis (1992–1996, 1997–2001); pN staging technique (lymph node dissection, sentinel biopsy); patient age at diagnosis (continuous); histologic type (ductal, lobular, tubular, other); tumour grade (1, 2, 3, unknown); and tumour size. At each step, the independent variables were entered in block.

## Results

Table 2 shows the main patient characteristics according to detection mode. Interval cancer patients were younger than patients with SD cancer. The distribution by number of previous negative mammographies did not differ substantially between the study subgroups. Also shown in Table 2 is that interval cancers were larger, of higher grade, and more likely to be of the lobular type. The bottom row of the table shows that interval cancers, particularly those diagnosed during the second interval year, were more often associated with lymph node metastases.

Table 3 shows the findings of forward stepwise logistic regression analysis. The upper row of the table gives the unadjusted ORs of lymph node metastases for interval cancers

Table 2
Characteristics of screen-detected cancers and interval cancers ($n = 2002$)

| | SD cancers | Interval cancers by interval month | | | $p$ |
|---|---|---|---|---|---|
| | ($n = 1211$) | 1–12 | 13–18 | 19–24 | |
| | | ($n = 273$) | ($n = 265$) | ($n = 253$) | |
| Median patient age (years) | 62 | 59 | 58 | 60 | 0.000[a] |
| Number of previous negative mammographies (%) | | | | | 0.014 |
| 1 | 70.9 | 67.0 | 69.1 | 73.5 | |
| 2 | 17.3 | 25.3 | 19.2 | 16.2 | |
| 3 | 9.0 | 3.3 | 8.7 | 7.1 | |
| 4–5 | 2.9 | 4.4 | 3.0 | 3.2 | |
| Tumour grade (%)[b] | | | | | 0.000 |
| 1 | 27.4 | 14.5 | 17.3 | 17.5 | |
| 2 | 50.3 | 47.5 | 45.5 | 42.9 | |
| 3 | 22.3 | 38.0 | 37.3 | 39.6 | |
| Unknown | 10.2 | 11.4 | 17.0 | 14.2 | |
| Tumour size (%)[c] | | | | | 0.000 |
| 2–7 mm | 17.0 | 5.1 | 6.8 | 6.7 | |
| 8–12 mm | 32.9 | 18.7 | 23.4 | 19.8 | |
| 13–17 mm | 24.5 | 27.5 | 26.0 | 21.7 | |
| 18–22 mm | 14.6 | 19.4 | 21.1 | 24.1 | |
| 23–27 mm | 4.5 | 11.0 | 9.4 | 9.9 | |
| ≥28 mm | 6.4 | 18.3 | 13.2 | 17.8 | |
| Histologic type (%) | | | | | 0.10 |
| Ductal | 76.9 | 73.3 | 72.1 | 74.3 | |
| Lobular | 15.8 | 21.6 | 21.9 | 18.2 | |
| Tubular | 2.9 | 1.1 | 1.1 | 2.0 | |
| Other | 4.5 | 4.0 | 4.9 | 5.5 | |
| Sentinel lymph node biopsy (%) | 27.0 | 13.6 | 17.4 | 19.8 | 0.000 |
| Positive lymph nodes (%) | 27.7 | 37.7 | 42.3 | 44.3 | 0.000 |

SD: screen-detected cancers.
[a] For the Kruskal–Wallis test. All other $p$ values are for the Pearson $\chi^2$ test.
[b] The percents of grade 1–3 cancers were calculated excluding those cancers with grade unknown.
[c] Criteria for categorisation are given in the Methods section.

Table 3
Odds ratio (and 95% confidence interval) for interval cancers versus the screen-detected cancers having positive lymph nodes, by interval month ($n = 2002$)

| Model | Variables in the model | Interval month | | |
|---|---|---|---|---|
| | | 1–12 | 13–18 | 19–24 |
| Basic | Detection mode | 1.58 (1.20–2.09) | 1.91 (1.45–2.52) | 2.08 (1.57–2.74) |
| 1 | Basic model + health area + time period of diagnosis | 1.61 (1.21–2.12) | 1.96 (1.49–2.59) | 2.06 (1.55–2.72) |
| 2 | Model 1 + pN staging technique | 1.48 (1.12–1.96) | 1.84 (1.39–2.44) | 1.95 (1.47–2.59) |
| 3 | Model 2 + patient age at diagnosis | 1.41 (1.06–1.87) | 1.74 (1.31–2.31) | 1.91 (1.43–2.54) |
| 4 | Model 3 + histologic type | 1.35 (1.01–1.81) | 1.70 (1.27–2.26) | 1.94 (1.45–2.59) |
| 5 | Model 3 + tumour grade | 1.23 (0.92–1.65) | 1.58 (1.18–2.12) | 1.73 (1.29–2.32) |
| 6 | Model 3 + tumour size | 0.95 (0.70–1.29) | 1.34 (0.99–1.81) | 1.37 (1.01–1.85) |
| 7 | Model 3 + tumour grade + tumour size | 0.91 (0.67–1.24) | 1.33 (0.98–1.80) | 1.35 (0.99–1.84) |
| 8 | Model 3 + histologic type + tumour grade + tumour size | 0.90 (0.66–1.22) | 1.33 (0.98–1.81) | 1.39 (1.02–1.89) |

Odds ratios were estimated using binary logistic regression analysis (forward stepwise method).

compared with SD cancers. Adjustment for health area of residence and time period of diagnosis (model 1) had a marginal impact on results.

The pN staging technique was found to be a confounder of some importance, since its inclusion (model 2) decreased the OR of positive lymph nodes by 10% (for interval cancers diagnosed 19–24 months after a negative mammography) to about 20% (for first-year interval cancers). The confounding occurred because the sentinel lymph node biopsy (versus dissection) predicted significantly the absence of lymph node metastases (data not shown) and was less frequent among interval cancers than SD cancers (Table 2).

When the patient age was adjusted for (model 3), the ORs of lymph node metastases showed a further, albeit moderate, decrease. This effect was accounted for by the inverse association of patient age with the prevalence of lymph node metastases (data not shown) coupled with the fact that interval cancer patients were younger than patients with SD cancer (Table 2).

ORs from model 3 were assumed as the baseline for assessing the effect of tumour characteristics. Histologic type, tumour grade, and tumour size were entered in turn into the model. The histologic type (model 4) was a modest confounder for interval cancers diagnosed within 18 months of negative mammography. This was probably due to their greater prevalence of lobular carcinoma (Table 2), that is, the cancer type most often associated with lymph node metastases (data not shown).

With adjustment for tumour grade (model 5), the OR of lymph node metastases decreased by about 45% for cancers that arose during the first interval year, and by about 20% for those presenting later. The confounding effect was clearly related to the unfavourable tumour grade distribution of interval cancers compared with SD cancers. An excess risk of lymph node metastases was still observed for all subgroups of interval cancers, although the level of significance was lower for those diagnosed in the first year.

Model 6 demonstrated that tumour size was the stronger confounder of the association between the detection mode and nodal status. In particular, tumour size alone explained all of the excess risk of lymph node metastases for the first-year interval cancers, with a drop from an OR of 1.41 to an OR of 0.95. For both groups of interval cancers arising in the second year, the OR decreased only by 55–60% and remained above unity -although at a borderline level of significance.

Model 7 confirmed that tumour grade played a minor confounding role as compared with tumour size. Model 8 was simultaneously adjusted for all covariates, with outcomes similar to those of model 6 and 7. Overall, the second-year interval cancers had an independent increase of approximately one-third in the risk of lymph nodes metastases.

## Discussion

Under the assumptions made, the study hypotheses were confirmed. Regarding the first-year interval cancers, most of which have previously been suggested to be false-negative cancers,[9–11] the observed confounding by tumour size showed that their excess risk of lymph node metastases was only a consequence of their higher chronological age. This is equivalent to saying that early-presenting interval cancers are not qualitatively different from SD cancers, and that those mammographic features underlying the false-negative diagnosis have no adverse biological implications. As to tumour grade, it is possible that its confounding effect in model 5 reflected primarily its tendency to increase with increasing tumour size.[20,23]

Among cancers surfacing in the second interval year, mainly comprised of true interval cancers according to previous reports,[9–11] the chronological age was confirmed to exert a stronger confounding effect than tumour grade. Both factors, however, failed to entirely explain the excess risk of lymph node involvement. This suggested that the increased aggressiveness of this subset of interval cancers was partly accounted for by intrinsic biological attributes, and that these were unrelated to chronological age and tumour grade as well.

In addition to potential unadjusted confounding factors, epidemiological biases, and data inaccuracies (see below), the possibility of alternative interpretations of results is inherent in the fact that the complexity of this matter cannot be captured by a few assumptions. In particular, the idea that tumour size is a proxy of its chronological age[8] assumes that tumour growth follows a linear pattern, which is only an approximation to the natural history of breast cancer. A number of tumour and host factors interact to determine the rate of tumour growth over time. This is generally described as an exponential growth phase followed by a deceleration asymptotically approaching a limiting tumour size, although many modified models have recently been developed.[24] Also relevant to the endpoint of the present study -the risk of lymph node metastases- is the fact that various models exist which relate tumour size to the initiation time of metastatic growth.

A related weakness in the study design should be noted. Tumour size was treated as a confounding factor for the relative risk of interval cancers having lymph node metastases, and the excess risk that was not explained by their size was attributed to their biological aggressiveness. In fact, tumour size itself increases with increasing biological aggressiveness, that is, it qualifies both as a confounder and an intermediate factor between the expression of an aggressive behaviour and the outcome variable. As a consequence, adjusting for tumour size might have caused a spuriously reduced estimate of the residual excess risk of lymph node metastases.

It can be hypothesised that hormone replacement therapy (HRT) use exerted some confounding effect upon the different patterns of risk of lymph node involvement for first- and second-year interval cancers. HRT use is associated with more favourable prognostic features of breast tumours,[25] and with decreased mammography sensitivity as well.[26] Although the latter might well depend on an increase in breast density, the close clinical surveillance of HRT users between regular screens is thought to increase the rate of interval cancers and to shorten their time to diagnosis.[27] In fact, the excess incidence of interval cancers for HRT users versus non-users is greater during the first year after screening mammography.[28]

Published studies with which to compare our results are scarce, and many have been flawed by small sample size and analysis limitations. At least three studies have reported an overrepresentation of adverse prognostic features among early-presenting interval cancers.[1–3] Conversely, despite differences in design and purposes, our results have interesting analogies with those of a large study of factors associated with the excess risk of interval cancer among premenopausal versus postmenopausal women.[29] An increased breast density was found to largely explain decreased mammography sensitivity at 12 months, whereas rapid tumour growth contributed substantially to decreased sensitivity at 24 months.

Our results were obtained from a case series that was free of the length bias arising from contamination with prevalent, slow-growing cancers.[20] We excluded from the study those cancers detected by a prevalence mammography or by a repeat mammography three or more years after the previous one, as well as the third-year interval cancers. Incidentally, it must be noted that the distribution by number of previous negative mammographies was similar between SD and interval cancers. This means that the two subpopulations of cancers resulted from a comparable screening experience, and had the same cumulative chance of being detected or missed by mammography.

We do also believe that our results were to a large extent free of the biasing effects of rescreening. In the last six-month period of the two-year interscreening interval, the risk of a cancer surfacing clinically was affected by the competing risk of diagnosis by repeat mammography. In line of principle, interval cancers actually observed in that time period were the result of a selection process, with the possibility of an artifactual change of unpredictable direction in their average level of biological aggressiveness. In fact, we assumed that the magnitude of these effects was a marginal one. Our main argument was that most cancers detected by screening 19–24 months after last negative screen would have clinically arisen much later.[22] In addition, since the calendaring of screening invitations does not reflect epidemiological considerations, the potential interval cancers picked up by rescreening may be taken to represent a roughly random sample of the whole. For this reasons, the last six-month period of the interscreening interval was retained into the study, though with separate analyses. The similarity of results for the two halves of the second interval year provided an *a posteriori* support for our approach.

There are other potential limitations to this study that warrant mention. First, the use of lymph node status as the sole indicator of biological aggressiveness of breast cancer[17,18] may be questionable. On the other hand, many of the known or putative biological markers of the disease are not fully

established nor adequately standardised in the routine care, nor are they accessible to cancer registries on a large scale.

Second, inaccuracies may have arisen from the reported date of diagnosis of interval cancers. The date recorded by cancer registries is the date of first pathology report or first hospital admission and not that of the onset of symptoms. This causes a forward temporal migration of interval cancers,[30] part of which are systematically shifted from the real incidence year to the next. Given the observed results, however, the partial misclassification of first-year interval cancers into the second year can only have eroded the difference in nodal status between the two subpopulations of patients.

Third, a sampling bias might have resulted from the inclusion criteria. The final analysis comprised 2002 patients. Six hundred and forty-nine more patients were excluded due to missing information alone, for a total number of 2651 patients potentially eligible for analysis. By implication, the study results were obtained from 75% of this theoretical population. According to the incomplete data available, the cancers excluded from analysis were of smaller tumour size and of lower histological grade than the 2002 cancers included. The distribution by detection mode, however, was similar between the two groups.

Fourth, we categorised tumour size in an unconventional fashion, that is, into clusters around 5 mm and multiples of 5 mm. As described elsewhere,[18] there is a tendency for the pathologists in the study area to render this variable as discrete multiples of 5 mm. This hinders using tumour size as a continuous variable as well as choosing cut-offs at multiples of 5 or 10 mm.[31] Our method, however, has the drawback that this study cannot be exactly replicated in those settings where only the standard TNM classification is available.

## Conclusion

We can confirm the hypothesis that there exists a relationship between the time since last negative screen and the biological aggressiveness of interval-surfacing cancers. The second interval year, but not the first, was associated with an excess risk of lymph node metastases that was independent from tumour size and grade. The results of this study improve the understanding of the screening process, particularly the interplay between mammography sensitivity and the natural history of breast cancer.

## Conflict of interest statement

None declared.

## Role of the funding source

This study was supported in part by research grants from the Italian Ministry of Health, Rome, and the Italian League against Cancer, Rome. The sponsors had no role in the collection, analysis and interpretation of data, in the writing of this report, and in the decision to submit the manuscript for publication.

## Acknowledgments

The membership of the IMPACT working group was as follows: 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, Department of Health, Regione Emilia-Romagna, Bologna); S. Ferretti (Ferrara Cancer Registry, Dipartimento di Medicina Sperimentale e Diagnostica, Sezione di Anatomia, Istologia e Citologia Patologica, Università di Ferrara, Ferrara); G.P. Baraldi (Breast Cancer Screening Programme, Ferrara); M. Federico, C. Cirilli (Modena Cancer Registry, Modena); R. Negri (AUSL, Modena); V. De Lisi, P. Sgargi (Parma Cancer Registry, Parma); A. Traina, M. Zarcone (Department of Oncology, ARNAS Ascoli, Palermo); A. Cattani, N. Borciani (AUSL, Reggio Emilia); L. Mangone (Registro Tumori di Reggio Emilia, Dipartimento di Sanità Pubblica, AUSL, Reggio Emilia); F. Falcini, A. Ravaioli, R. Vattiato, A. Colamartini (Romagna Cancer Registry, IRST, Forlì); M. Serafini, B. Vitali, P. Bravetti (AUSL, Ravenna); F. Desiderio, D. Canuti, C. Fabbri (AUSL, Rimini); A. Bondi, C. Imolesi (AUSL, Cesena); N. Collina, P. Baldazzi, M. Manfredi, V. Perlangeli, C. Petrucci, G. Saguatti (AUSL, Bologna); N. Segnan, A. Ponti, G. Del Mastro, C. Senore, A. Frigerio, S. Pitarella (CPO Piemonte, AO San Giovanni Battista, Torino); S. Patriarca, R. Zanetti (Registro Tumori Piemonte, CPO Piemonte, AO San Giovanni Battista, Torino); M. Vettorazzi, M. Zorzi (Venetian Tumour Registry, Istituto Oncologico Veneto, Padova); A. Molino, A. Mercanti (Università di Verona, Verona); R. Mariotto (Azienda ULSS, Verona); R. Tumino, A. Sigona (Registro Tumori, UO Anatomia Patologica, Azienda Ospedaliera Civile MP Arezzo, Ragusa); G. La Perna, C. Iacono, ONCOIBLA – UO di Oncologia, AO Ragusa, Ragusa); F. Stracci, F. La Rosa (Registro Tumori Umbro, Perugia); M. Petrella, I. Fusco Moffa (Epidemiology Unit, ASL2, Perugia).

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