Interval Breast Cancer Versus Screen-Detected Cancer: Comparison of Clinicopathologic Characteristics in a Single-Center Analysis

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Abstract

Interval breast cancers (IBC) have been of great concern since breast mammogram screening programs were introduced. We compared IBC to screen-detected cancers (SDC). IBC accounted for one-fifth of all breast cancers diagnosed in women who followed the regional screening program. IBC appeared to be more aggressive than SDC in terms of tumor invasiveness, size, and St Gallen molecular subtype, leading to worse overall and disease-free survival.

Background: The introduction of breast screening programs has raised the problem of interval breast cancers (IBC). The aims of this study were to analyze the impact of IBC on the screening program, to compare IBC and screen-detected cancers (SDC), and to identify possible predictors of mortality. **Patients and Methods:** Patients with breast cancer diagnosed during the regional breast screening program between January 2008 and December 2013 at a single center in Italy were included. Demographic, preoperative, and postoperative data were prospectively collected and retrospectively analyzed. **Results:** Five hundred thirty-four patients were enrolled; 106 women (19.9%) had IBC and 428 women (80.1%) SDC. IBC presented more aggressive features compared to SDC, such as tumor invasiveness (95% vs. 85%; $P = .005$), tumor size ($\geq$ pT2 37% vs. 21%; $P = .001$), grade (G3 39% vs. 17%; $P < .001$), and St Gallen molecular subtype (triple negative 22% vs. 7%; $P < .001$), resulting in higher distant recurrence rate (8% vs. 2%; $P = .009$) and worse overall and disease-free survival ($P = .03$ and $P = .001$, respectively). Cox multivariate regression analysis identified St Gallen molecular subtype as the only predictor of mortality in patients with breast cancer ($P = .03$). **Conclusion:** IBC accounted for one-fifth of all breast cancers diagnosed in women who followed the regional screening program. Furthermore, IBC appeared to have more aggressive features compared to SDC, leading to worse survival. These worse survivals depended on St Gallen molecular subtype.

Introduction

The American Cancer Society estimated that in 2016, breast cancer would be the first tumor discovered in new cancer cases occurring in women in the United States, causing more than 40,000 deaths and remaining the second leading cause of cancer-related death among women.[1] The introduction of mammogram screening allowed breast cancers to be detected at earlier stages,[2] thus improving patients' prognosis[3] thanks to a breast cancer–related mortality reduction of 26%.[4] Moreover, the screening program led to more favorable tumor characteristics in terms of tumor size, lymph node (LN) involvement, and hormone status.[5]

Besides this prognostic improvement, the screening program raised 2 main problems: overdiagnosis of ductal carcinoma-in-situ and interval breast cancers (IBC).[6-9] IBC are defined as in-situ or invasive breast cancers diagnosed after a negative mammographic screening examination and before the next recommended routine screening mammogram.[10-12] The literature has demonstrated that IBC are more aggressive than screen-detected cancers (SDC) in terms of tumor size, LN involvement, grade, and molecular features.[10,13-18]

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The aims of this study were to analyze the impact of IBC on the screening program, to compare IBC and SDC in terms of clinical and pathologic characteristics, and to identify possible predictors of mortality in patients with breast cancer diagnosed during the screening program period.

Methods

This retrospective single-center cohort analysis was conducted on prospectively recorded data extracted from the database of the Breast Unit of Trieste, Italy. The database collected all patients with both benign and malignant breast pathologies since 2004. Data on patients' follow-up and causes of death were retrieved from the Computerized Medical Records of the Azienda Sanitaria Universitaria Integrata di Trieste.

Inclusion and Exclusion Criteria

This study included women diagnosed with either ductal carcinoma-in-situ and invasive cancer who followed the regional mammographic screening program in Trieste, involving women aged 50 to 69 years assessed biennially between January 2008 and December 2013.

Since the regional mammographic screening program started in January 2006, patients diagnosed with cancer in the first biennium (ie, 2006 to 2007, the first prevalence round) were not included in this study to reduce the bias due to the more aggressive breast cancers diagnosed at the beginning of the screening program. Patients following the screening program between 2014 and 2015 were not included in this study in order to not negatively influence the ratio between IBC and SDC, because IBC could be diagnosed until December 2017. Women who underwent screening mammograms after January 2016 were not included because the round is not yet completed.

Patients who had not undergone a screening mammogram within the previous 2 years and those who had a history of breast cancer were excluded.

Women included in this study were divided in 2 groups according to the timing of tumor diagnosis: patients with cancers diagnosed during a screening mammogram were classified as SDC, and those who had cancers diagnosed within the 2 years after a negative screening mammogram were identified as IBC.

Parameters Evaluated

The 2 groups were compared in terms of age, family history of breast cancer, breast density at mammogram, tumor type and histology, surgical procedure performed, pT, pN, stage, grade, Ki-67, molecular subtype according to St Gallen criteria, adjuvant therapy, radiotherapy, and survival.

Overall survival (OS) was calculated from the date of surgery (or diagnostic biopsy for women without surgery) to the date of last follow-up or death from any cause. Disease-free survival (DFS) was calculated from the date of surgery (or diagnostic biopsy for women without surgery) to the date of last follow-up or to the date of local or distant metastasis. Deadline of follow-up for survival analysis was set to October 2016.

The entire cohort was divided according to St Gallen molecular subtype into luminal and nonluminal cancers, and OS was calculated for these 2 subcohorts.

Preoperative Evaluation

All patients underwent a mammogram and a breast ultrasound (US). The Breast Imaging Reporting and Data System (BI-RADS) of the American College of Radiology was used to refer to breast composition categories and to assessment categories for mammogram, US, and magnetic resonance imaging.[19]

US-guided fine-needle aspiration cytology or stereotactic biopsy was performed in all suspected breast lesions to obtain a definitive diagnosis. If certain diagnosis was not reached or if the lesion was $>$ 3 cm, a US-guided core needle biopsy with molecular subtype evaluation was carried out. Patients with high-density breast tissue (ie, BI-RADS C and D), breast microcalcifications, lobular breast cancers, and/or tumors $>$ 4 cm underwent magnetic resonance imaging. Patients with triple-negative cancers and/or tumors $>$ 5 cm proceeded to staging contrast-enhanced thoracoabdominal computed tomography, bone scintigraphy, and positron emission tomography.

Axillary US was always performed before surgery to evaluate LN status. If abnormal LNs were found, fine-needle aspiration cytology was carried out.

Women with a definitive diagnosis of breast cancer were invited to undergo a clinical breast examination with a breast surgeon. During the visit, a complete history of the patient was collected, and a clinical examination of breasts and axillary LNs was performed.

All patients were offered pre- and postoperative psychological support.

Surgical Procedure

All cases were evaluated and analyzed preoperatively during the multidisciplinary meeting of the Breast Unit of Trieste, officially recognized by the European Society of Mastology in 2016.

Women with high-stage, triple-negative, or human epidermal growth factor receptor 2 (HER-2)-positive breast cancers were referred to neoadjuvant chemotherapy. The surgical procedure was decided after evaluating the breast volume—tumor dimension ratio, molecular subtype (when available), and patient preference. Patients underwent breast conservation surgery (ie, quadrantectomy) or mastectomy, mainly skin or nipple sparing. Immediate or delayed breast reconstruction was usually carried out by plastic surgeons after nonconservative breast surgery.

Patients with clinically negative LNs underwent sentinel LN biopsy. Lymphoscintigraphy was performed the day before surgery in all these patients, and the radioactive axillary sentinel LN was localized by gamma probe. Sentinel LNs touch imprint cytologic analysis was performed intraoperatively to detect axillary metastases. Women with preoperative LNs involvement or positive sentinel LN biopsy proceeded to axillary node dissection. All surgical procedures were performed by 2 expert breast surgeons.

All patients signed informed consent preoperatively for the surgical procedure and for data collection.

Postoperative Staging

Breast cancer stage was defined according to the American Joint Committee on Cancer.[20] Tumor type was recorded according to the World Health Organization classification of breast tumors.[21] The histologic grade was assessed using the Nottingham system.[22]

Immunohistochemistry (IHC) was performed preoperatively in case of fine-needle aspiration biopsy and postoperatively in each

surgical specimen. Estrogen receptor (ER) and progesterone receptor (PR) status, HER-2 status, and cell proliferation activity in terms of Ki-67 were determined by IHC. According to the American Society of Clinical Oncology, ER and PR status were considered positive if at least 1% of cells were positive at IHC.[23] HER-2 was scored 3+ when there was a strong circumferential membranous staining in more than 30% of invasive carcinoma cells, 2+ when a moderate circumferential membranous staining in more than 10% of invasive carcinoma cells was recorded, 1+ when a weak and incomplete circumferential membranous staining was found in more than 10% of invasive carcinoma cells, and 0 when no staining was registered. A HER-2 score of 0 and 1+ was considered negative, and a HER-2 score of 3+ was defined positive. Tumors scored as 2+ were considered equivocal, and HER-2 status was then determined using fluorescence in-situ hybridization.[10,23] Ki-67 values were measured as the percentage of positively stained malignant cells among the total number of tumor cells assessed. A Ki-67 cutoff point of 20% was defined to separate low from high proliferation grade.[24] Tumors were classified according to the St Gallen 2013 guidelines. Molecular subtypes were reported as follows: luminal A (ER and PR positive, Ki-67 < 20%, HER-2 negative), luminal B—HER-2 negative (ER positive, PR positive or Ki-67 < 20%, HER-2 negative), luminal B—HER-2 positive (ER and/or PR positive, any Ki-67, HER-2 positive), HER-2 type (ER and PR negatives, any Ki-67, HER-2 positive), or triple negative (ER, PR, and HER-2 negative, any Ki-67).[25]

Adjuvant Therapy

Postoperative therapy was decided according to international guidelines.[25,26] Tumor stage, molecular subtype, and patient age were the main parameters considered to decide which kind of adjuvant therapy to provide.

Patients with positive hormone receptors were treated with endocrine therapy (eg, tamoxifen, anastrazole), while patients with Ki-67 > 20% and/or with triple-negative cancers received adjuvant chemotherapy. Patients with HER-2—positive cancers were treated with an association of chemotherapy and anti—HER-2 monoclonal antibodies (ie, trastuzumab).

Breast radiotherapy was provided to all patients who underwent conservative breast surgery. Radiotherapy was provided postoperatively with or without intraoperative radiotherapy as an anticipated boost of radiation. Patients underwent chest radiotherapy in cases of tumors > 5 cm, tumor infiltrating the chest wall, positive internal mammary LNs, or > 4 positive axillary LNs at lymphadenectomy.

All patients undertook a follow-up program at the Department of Oncology with annual breast examination, mammogram, and breast US for at least 5 years.

Statistical Analysis

Quantitative data are reported as mean, median, standard deviation, and interquartile range [25th-75th percentile]. Qualitative variables are expressed as absolute frequencies and percentages. Differences in categorical data were compared by the chi-square test or the Fisher exact test, as appropriate. Differences in continuous variables (age at diagnosis) were compared by the Mann-Whitney test. Univariate analyses of OS and DFS rates were performed by the Kaplan-Meyer method. Differences between survival curves were analyzed by the log-rank test (Mantel-Cox). Cox regression analysis was performed to identify possible prognostic factors (univariate and multivariate analysis with adjustment for confounders). Results are reported as hazard ratios and 95% confidence intervals. A level of 5% was set for statistical significance. Statistical analyses were carried by R 3.0.3 software (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/).

Results

Comparison of Preoperative, Operative, and Postoperative Parameters

Table 1 summarizes the parameters analyzed.

A total of 534 patients, 106 IBC (19.9%) and 428 SDC (80.1%), were identified. Among the IBC group, 1 patient had a bilateral breast cancer, whereas 12 patients had bilateral involvement in the SDC group. The median age was 62 and 64 years for the IBC and SDC groups, respectively ($P = .09$).

Patients with at least one first-degree relative with breast cancer comprised 30% of the IBC group and 18% of the SDC group ($P = .02$).

The breast density, according to the BI-RADS classification, registered at the diagnostic mammogram showed that patients with IBC had more high-density breasts than patients with SDC (BI-RADS C and D, 45% and 25%, respectively; $P < .001$).

Twenty patients, 9 with IBC and 7 with SDC, were treated with chemotherapy alone and did not undergo surgery.

The type of surgery performed statistically differed between the 2 groups, with 78% of IBC patients undergoing breast-conserving surgery (ie, quadrantectomy) compared to 88% of SDC patients ($P = .001$). LN surgery in terms of axillary dissection was carried out more often in the IBC group compared to the SDC group (31% and 24%, respectively), but these data were not statistically significant ($P = .20$).

Invasive cancers were the most common tumor type in both groups, accounting for 95% of IBC and 85% of SDC ($P = .005$). Invasive ductal cancer was less commonly found in IBC compared to SDC (66% vs. 74%; $P = .01$), whereas invasive lobular cancers were equally distributed between the 2 groups (23% vs. 22%, respectively). One IBC patient had lymphoma, 2 SDC patients had lymphoma, and 1 SDC patient had a phylloid tumor. These 4 patients were excluded from the analysis.

Of IBC, 37% were > 2 cm in size compared to SDC, of which only 21% had dimensions > 2 cm ($P = .001$).

Most patients in both groups did not have LN involvement. IBC were node positive in 24% of patients compared to 17% of patients with SDC; this difference was not statistically significant.

Staging statistically differed between the 2 cohorts ($P < .001$), with a prevalence of stage I tumors in the SDC group (69% vs. 55%; $P = .01$) and stage IV cancers in the IBC group (9% vs. 1%; $P < .001$). However, both groups had mainly stage I and II cancers.

IBC were poorly differentiated in 39% of patients, whereas SDC were classified as G3 in 17% of cases ($P < .001$).

For molecular subtypes, according to St Gallen classification,[25] IBC had a more aggressive pattern than SDC. Of the IBC, 35% were classified as luminal A, 25% as luminal B—HER-2 negative, 9% as luminal B—HER-2 positive, 9% as HER-2 positive, and 22%

Table 1 Preoperative, Operative, and Postoperative Parameters Evaluated

Variable	IBC (107 Cancers in 106 Women)	SDC (440 Cancers in 428 Women)	*P*
Age (y)			
Mean (± SD)	63 ± 11	63 ± 6	.09
Median [25th-75th percentile]	62 [57-68]	64 [59-68]	
Family History of Breast Cancer			.02
None	59 (59%)	280 (70%)	
First-degree relative	30 (30%)	72 (18%)	
Second-degree relative	11 (11%)	48 (12%)	
Unknown	6	28	
BI-RADS			
A-B	53 (55%)	320 (75%)	<.001
C and D	44 (45%)	105 (25%)	
Unknown	9	3	
Breast Surgery			.001
Conservative	76 (78%)	381 (88%)	
Mastectomy	22 (22%)	52 (12%)	
None	9	7	
Lymph Node Surgery[a]			.20
Only sentinel procedure	68 (69%)	325 (76%)	
Axillary dissection	30 (31%)	104 (24%)	
Unknown	3	0	
Tumor Type			.005
Invasive	101 (95%)	371 (85%)	
In situ	5 (5%)	64 (15%)	
Unknown	1	5	
Invasive Cancer Histology Subtype[b]			.01
Ductal	67 (66%)	279 (74%)	
Lobular	23 (23%)	81 (22%)	
Other (eg, medullary, tubular, papillary)	12 (11%)	16 (4%)	
Tumor Size (pT)[c]			.001
pT1a-b	23 (23%)	142 (38%)	
pT1c	41 (41%)	153 (41%)	
pT2+	37 (37%)	76 (21%)	
Lymph Node Status (pN)[a]			
N0	68 (69%)	325 (76%)	.28
N1mi	6 (6%)	29 (7%)	
N+	24 (25%)	75 (17%)	
Unknown	3	0	
Stage[c]			
I	55 (55%)	249 (69%)	<.001
II	26 (26%)	92 (25%)	.01
III	10 (10%)	18 (5%)	.89
IV	9 (9%)	2 (1%)	.06
Unknown	1	10	<.001
Grade[c]			
G1	9 (9%)	49 (14%)	<.001
G2	51 (52%)	250 (69%)	
G3	39 (39%)	62 (17%)	
Unknown	2	10	
Proliferative Index Ki-67[c]			
Ki-67 ≥20%	52 (53%)	122 (34%)	<.001
Ki-67 <20%	46 (47%)	241 (66%)	
Unknown	3	8	
Molecular Subtype[c]			
Luminal A	34 (35%)	173 (48%)	<.001
Luminal B—HER-2 negative	24 (25%)	129 (36%)	
Luminal B—HER-2 positive	9 (9%)	17 (5%)	
HER-2 positive	9 (9%)	15 (4%)	
Triple negative	21 (22%)	26 (7%)	
Unknown	4	11	
Adjuvant Therapy			
Chemotherapy	58 (55%)	101 (24%)	<.001
Only hormone therapy	42 (40%)	259 (62%)	
None	6 (5%)	58 (14%)	
Unknown	0	10	
Radiotherapy			
Yes	77 (73%)	360 (86%)	.002
No	29 (27%)	60 (14%)	
Unknown	0	8	
Local Recurrence			
Yes	3 (3%)	7 (2%)	.42
No	103 (97%)	421 (98%)	
Distant Recurrence			
Yes	8 (8%)	9 (2%)	.009
No	98 (92%)	419 (98%)	
Follow-up			
Disease-free	91 (86%)	394 (92%)	.09
Alive with tumor	4 (4%)	6 (1%)	
Dead	11 (10%)	28 (7%)	
Cause of Death			
Breast cancer	10 (91%)	14 (50%)	.02
Other	1 (9%)	14 (50%)	

Abbreviations: BI-RADS = Breast Imaging Reporting and Data System; HER-2 = human epidermal growth factor receptor 2; IBC = interval breast cancer; SDC = screen-detected cancer.

[a]Lymph node surgery was performed in all invasive cancers and in ductal carcinoma-in-situ with high-grade dysplasia.

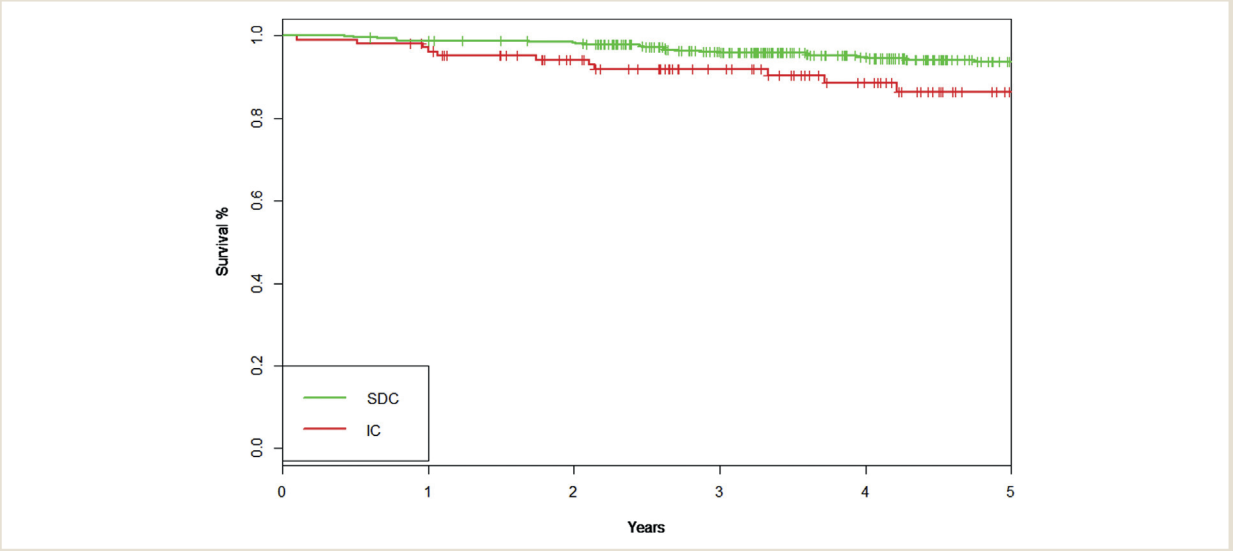
[b]One IBC patient and 5 SDC patients had 2 different histologic types of tumor.

[c]Data evaluated for invasive breast cancers only.

as triple negative compared to SDC, which were 48% luminal A, 36% luminal B—HER-2 negative, 5% luminal B—HER-2 positive, 4% HER-2 positive, and 7% triple negative. The difference in this distribution appeared to be statistically significant ($P < .001$).

Patients with IBC were treated more often with adjuvant chemotherapy, whereas patients with SDC usually received only hormone therapy ($P < .001$). Breast radiotherapy was provided to 73% of IBC patients and 86% of SDC patients ($P = .002$).

Figure 1 Kaplan-Maier Survival Curve for Overall Survival



Abbreviations: IBC = interval breast cancers; SDC = screen-detected cancers.

The local recurrence rate was substantially the same in both groups (3% in IBC and 2% in SDC; $P = .42$), whereas the development of distant metastases during the follow-up was more frequent in the IBC group (8% vs. 2%; $P = .009$).

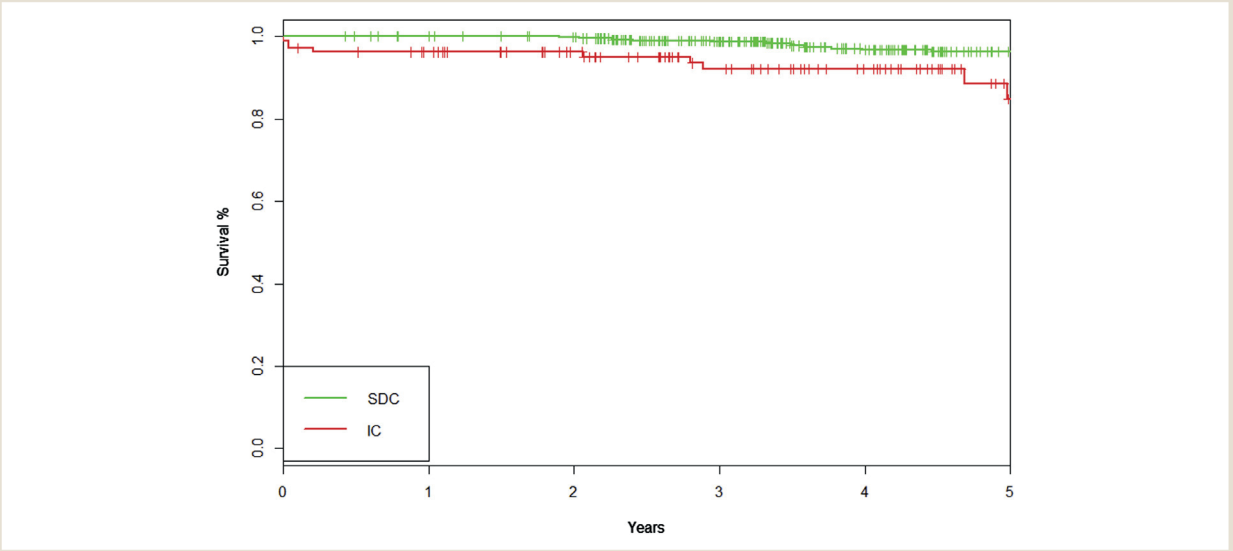
Thirty-nine patients, 11 (10%) IBC and 28 (7%) SDC, died during follow-up. Of the 11 patients belonging to the IBC group, 91% of deaths (10 patients) were due to breast cancer, compared to 50% (14 of 28 patients) of SDC patients ($P = .02$).

Survival Analysis

Figures 1 and 2 show the Kaplan-Maier survival curves for OS and DFS, respectively.

Every patient included in the OS analysis had a minimum of 36 days (1 patient died with metastatic breast cancer at diagnosis) to a maximum of 8 years of follow-up. The mean follow-up period for OS was 4.61 ± 1.89 years, and the median [25th-75th percentile] was 4.52 years [3.09-6.15]. The 5-year OS for IBC was 86%

Figure 2 Kaplan-Maier Survival Curve for Disease-Free Survival



Abbreviations: IBC = interval breast cancers; SDC = screen-detected cancers.

compared to 94% for SDC ($P = .03$). After stratification of the cohort according to St Gallen molecular subtype, no statistically significant difference was found in 5-year OS for IBC and SDC in both luminal and nonluminal cancers (89% vs. 95%, $P = .40$ and 88% vs. 94%, $P = .32$, respectively).

Every patient included in the DFS analysis had a minimum of 14 days (patient with metastatic breast cancer at diagnosis) to a maximum of 8 years of follow-up. The mean follow-up period for DFS was 4.55 ± 1.92 years and the median [25th-75th percentile] was 4.47 years [3.07-6.13]. The 5-year DFS for IBC was 85% compared to 96% for SDC ($P = .001$).

Univariate and Multivariate Analysis

The results of the univariate and multivariate Cox regression analyses are reported in Tables 2 and 3, respectively.

Cox regression analysis was carried out to identify possible predictors of mortality in patients with breast cancer. In the Cox univariate analysis, screening detection mode was a favorable outcome (hazard ratio 0.46, 95% confidence interval 0.23-0.93; $P = .03$), whereas large tumors, positive node status, G3 grade, high Ki-67, and nonluminal tumors (mostly triple-negative breast cancers) were negative prognostic factors of mortality.

In multivariate analysis, after adjusting for other prognostic factors, only nonluminal molecular subtype was confirmed as a negative prognostic factor for mortality (hazard ratio 2.45, 95% confidence interval 1.08-5.55; $P = .03$).

Discussion

This study demonstrated and estimated the magnitude of the problem of IBC on the breast screening program. Interval cancers accounted for 19.9% of all breast malignancies diagnosed during the regional screening program period in patients undergoing the screening examinations. This result agrees with previously published data, which report the incidence of IBC to be between 10% and 32.49%.[27,28] The fourth edition of the European guidelines for quality assurance in breast cancer screening and diagnosis considered the IBC rate "desirable" as inferior to 30% during the first year after the negative screening mammogram and less than 50% during the second year.[29]

The results obtained from this study suggested that SDC have more favorable characteristics than IBC, which lead to better survival. Cancers diagnosed at the screening mammogram were less invasive, smaller, and better differentiated, and they had less aggressive molecular features. These characteristics explain the higher rate of breast-conserving surgery in SDC patients and the reduced administration of chemotherapy to these women.

Median age at diagnosis was lower in IBC patients compared to SDC patients. Although not statistically significant, this result is supported by other studies, which suggested that IBC more often involved younger women.[17,30-32] This hypothesis could be reinforced by the fact that patients with IBC had higher-density breasts (ie, BI-RADS C and D) at the diagnostic mammogram, a typical feature of younger patients.[33] A similar difference in breast density distribution between SDC and IBC groups has been reported elsewhere.[18,30,33,34] Boyd et al[35] stated that density found by mammogram is strongly associated with the risk of breast cancer detected by screening or between screening tests. Their results showed how the odds ratio for the risk of breast cancer detected less than 12 months after the last screening mammogram in patients with a density of 75% or more was 17.8 compared to the odds ratio of 3.5 for those detected during the screening program. Similar results were found by Porter et al.[36] A possible explanation for these

Table 2 Univariate Cox Regression Analysis

Variable	Hazard Ratio (95% Confidence Interval)	*P*
Mode of Detection		
Interval breast cancers	1.00 (Reference)	
Screen-detected cancers	0.46 (0.23-0.93)	.03
Tumor Size		
pT1	1.00 (Reference)	
pT2+	3.49 (1.85-6.60)	<.001
Node Status		
pN+	1.00 (Reference)	
pN0	0.343 (0.21-0.89)	.02
Grade		
G1/G2	1.00 (Reference)	
G3	2.36 (1.14-4.86)	.02
Ki-67 Status		
<20%	1.00 (Reference)	
≥20%	2.78 (1.44-5.37)	.002
St Gallen Molecular Subtype		
Luminal A	1.00 (Reference)	
Luminal B—HER-2 negative	2.50 (1.05-5.96)	.04
Luminal B—HER-2 positive	3.87 (1.16-12.86)	.02
HER-2 positive	2.49 (0.53-11.72)	.24
Triple negative	5.20 (2.01-13.50)	<.001
St Gallen Molecular Subtype[a]		
Luminal	1.00 (Reference)	
Nonluminal	2.60 (1.35-5.02)	.004

Abbreviation: HER-2 = human epidermal growth factor receptor 2.
[a]Luminal refers to luminal A and luminal B—HER-2-negative cancers; nonluminal refers to luminal B—HER-2 positive, HER-2 type, and triple-negative cancers.

Table 3 Multivariate Cox Regression Analysis

Variable	Hazard Ratio (95% Confidence Interval)	*P*
Mode of Detection		
Interval breast cancers	1.00 (Reference)	
Screen-detected cancers	0.96 (0.67-2.46)	.92
Tumor Size		
pT1	1.00 (Reference)	
pT2+	1.56 (0.67-3.59)	.30
Node Status		
pN+	1.00 (Reference)	
pN0	0.57 (0.25-1.26)	.16
St Gallen Molecular Subtype[a]		
Luminal	1.00 (Reference)	
Nonluminal	2.20 (1.01-4.83)	.03

[a]Luminal refers to luminal A and luminal B—HER-2-negative cancers; nonluminal refers to luminal B—HER-2 positive, HER-2 type, and triple-negative cancers.

results is that high-density breasts, which are typically found in younger women, could hide small cancers during the screening mammogram, which become evident later at a higher stage.[37] Ciatto et al[31] suggested as a possible solution to this problem shortening the time interval between screening mammograms or routinely using breast ultrasound to improve the sensitivity and efficacy of the screening program in patients with high-density breasts.

A family history of breast cancer is a well-known risk factor for developing of breast cancer in general.[8] Comparing SDC and IBC in terms of family history have conflicting results in literature.[8,16,33,36,38,39] Holm et al[16] reported an effect of family history on the risk of IBC, assuming a possible disparate genetic background of SDC and IBC. Our study confirmed this effect, suggesting women with a family history of breast cancer ought to be placed on a diagnostic path for patients at high risk. Moran et al[40] reported that lobular histology might be the cause of "missing" cancers at mammograms, resulting in higher rates of falsely negative mammograms. This result was used to justify the higher invasive lobular cancer rates in IBC compared to SDC (21.1% vs. 11.1%; $P < .05$).[10] Although our study reported a statistically significant difference in histology distribution, invasive lobular cancer rates were similar between IBC and SDC (23% vs. 22%, respectively).

IBC had features more likely to be aggressive, such as invasiveness, lesser differentiation, higher stage, and worse molecular characteristics (ie, high Ki-67, HER-2 positive, and triple negative). Most tumors diagnosed by mammograms are invasive cancers, and they accounted for 95% of IBC and 85% of SDC. These results appeared to be similar to the ones reported by Baré et al.[17] In the literature, IBC is described as being diagnosed at a higher stage compared to SDC.[10,36] This difference in staging may be the result of the larger dimensions of IBC compared to SDC.[10,17,18,24,36,41] This study showed that patients with LN involvement more often belonged to the IBC group, even if this difference was not statistically significant. Most studies[10,24,42] have found that patients with IBC have a higher risk of having LN metastases; Porter et al[36] reported similar but not statistically significant results ($P = .97$).

The larger dimensions of IBC lesions explain the lower rate of breast-conserving surgery and radiotherapy provided to these patients. Similarly, the comparable LN metastasis rate between the 2 groups justifies the similar trend in LN surgery with a prevalence in sentinel LN biopsy. In the literature, this difference in surgical approach to treat the primary cancer was evident, as was the difference in nodal surgery. Pálka et al[42] reported that 86.4% of SDC patients underwent breast-conserving surgery compared to 54.2% of IBC patients, and that axillary dissection was carried out in 53.1% of SDC and 79.2% of IBC patients ($P < .001$ in both cases).

IBC had higher Ki-67 and/or HER-2 expression and were more often triple negative than SDC. The differences in molecular features that we found are similar to the ones reported in literature.[17,18,38] Studies have demonstrated that Ki-67 expression is higher in IBC compared to SDC, and that Ki-67 of $\geq$ 20% is associated with an odds ratio of 2.11 to 4.[18,38] Meshkat et al[10] found that according to St Gallen molecular classification, SDC were mainly luminal A, whereas IBC accounted for more luminal B, HER-2 type, and triple-negative cancers.

The different molecular patterns identified in the 2 groups influenced the adjuvant therapeutic scheme patients had to follow. Therefore, chemotherapy was administered more often to IBC patients, whereas hormone therapy alone was mainly provided to SDC patients. These findings are in agreement with previously published data.[5,13,42]

Falck et al[24] compared mortality between symptomatic IBC and SDC in luminal A–like and non–luminal A–like subgroups. Their findings revealed that mortality was influenced by the type of diagnosis (ie, IBC and SDC) in luminal A–like cancers, but this was not confirmed for non–luminal A–like cancers. In our study, the OS after molecular stratification did not show any statistically significant difference between SDC and IBC. We reported that both 5-year OS and 5-year DFS were better for SDC compared to IBC, and both these findings were statistically significant. Rayson et al[13] reported similar results, demonstrating better OS and DFS for SDC compared to "true" IBC ($P = .0017$ and $P = .0016$, respectively).

In the present study, multivariate Cox regression analysis showed that nonluminal molecular subtype was the only independent predictor of mortality. Although van der Vegt et al[43] found that the molecular pattern did not reach the statistical significance in their multivariate analysis, our results appear to be comparable to findings reported by others.[15,24,38] This result could be explained by the fact that the poorer survival of patients with IBC is due to the higher number of nonluminal cancers in this group and not to the timing of the diagnosis per se.

Our study has several limitations. First, our study is retrospective, but this was the only mode of study we could prepare; it appears impossible to do otherwise. The second limitation is the incompleteness of some data as a result of the impossibility of recovering them all. Third, our cohort sample size, especially for IBC patients, is rather small. A fourth limitation lies in the study's duration of follow-up, which is too short to perform a good evaluation of the recurrence rate. Finally, we did not reevaluate the negative mammograms of IBC patients to learn whether they were "true" IBC, as other studies have done.[8,37,44,45]

The 2 main strengths of this study are the strict adherence to the IBC definition and the enrollment period, including 3 complete rounds of breast cancer screening and the following period during which patients could develop IBC. This well-defined enrollment period allowed us to determine the exact incidence of IBC in our population.

Larger studies are needed to confirm our results.

Conclusion

This retrospective study found that IBC accounted for one-fifth of all breast cancers diagnosed in women who followed the regional mammogram screening program in Trieste, Italy. These cancers appeared to have more aggressive histologic and molecular features compared to SDC, leading to worse survival. The poor survival seemed to depend on the nonluminal molecular subtype, which was more frequent in IBC.

Clinical Practice Points

- IBC are in-situ or invasive breast cancers diagnosed after a negative mammogram screening examination and before the next recommended routine screening mammogram.
- There is still no consensus about the aggressiveness of IBC.

- We analyzed 534 women who followed the regional breast screening program between January 2008 and December 2013; we found that 106 (19.9%) had IBC and 428 (80.1%) had SDC.
- IBC appeared to be more aggressive compared to SDC in terms of tumor invasiveness (95% vs. 85%), tumor size (≥ pT2 37% vs. 21%), grade (G3 39% vs. 17%), and St Gallen molecular subtype (triple negative 22% vs. 7%), resulting in a higher distant recurrence rate (8% vs. 2%) and worse 5-year OS and DFS (86% vs. 94% and 85% vs. 96%, respectively).
- Nonluminal molecular subtype were the only independent prognostic factor.
- The impact of IBC on the screening program and the higher aggressiveness of these tumors compared to SDC should lead to the creation of more sensible imaging techniques and to a specific diagnostic path for high-risk women.

Disclosure

The authors have stated that they have no conflict of interest.

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