Triple-Negative versus Non-Triple-Negative Breast Cancers in High-Risk Women: Phenotype Features and Survival from the HIBCRIT-1 MRI-Including Screening Study

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Abstract

Purpose: To compare phenotype features and survival of triple-negative breast cancers (TNBC) versus non-TNBCs detected during a multimodal annual screening of high-risk women.

Experimental Design: Analysis of data from asymptomatic high-risk women diagnosed with invasive breast cancer during the HIBCRIT-1 study with median 9.7-year follow-up.

Results: Of 501 enrolled women with BRCA1/2 mutation or strong family history (SFH), 44 were diagnosed with invasive breast cancers: 20 BRCA1 (45%), 9 BRCA2 (21%), 15 SFH (34%). Magnetic resonance imaging (MRI) sensitivity (90%) outperformed that of mammography (43%, P < 0.001) and ultrasonography (61%, P = 0.004). The 44 cases (41 screen-detected; 3 BRCA1-associated interval TNBCs) comprised 14 TNBCs (32%) and 30 non-TNBCs (68%), without significant differences for age at diagnosis, menopausal status, prophylactic oophorectomy, or previous breast cancer. Of 14 TNBC patients, 11 (79%) were BRCA1; of the 20 BRCA1 patients, 11 (55%) had TNBC; of 15 SFH patients, 14 (93%) had non-TNBCs (P = 0.007). Invasive ductal carcinomas (IDC) were 86% for TNBCs versus 43% for non-TNBCs (P = 0.010). G3 IDCs 71% versus 23% (P = 0.006), size 16 ± 5 mm versus 12 ± 6 mm (P = 0.007). TNBC patients had more frequent ipsilateral mastectomy (79% vs. 43% for non-TNBCs, P = 0.050), contralateral prophylactic mastectomy (43% vs. 10%, P = 0.019), and adjuvant chemotherapy (100% vs. 44%, P < 0.001). The 5-year overall survival was 86% ± 9% for TNBCs versus 93% ± 5% (P = 0.946) for non-TNBCs; 5-year disease-free survival was 77% ± 12% versus 76% ± 8% (P = 0.216).

Conclusions: In high-risk women, by combining an MRI-including annual screening with adequate treatment, the usual reported gap in outcome between TNBCs and non-TNBCs could be reduced.

Introduction

Triple-negative breast cancers (TNBC), defined as breast cancers testing negative to estrogen receptor (ER) and progesterone receptor (PR) in the absence of HER2 overexpression, form a heterogeneous clinical subset partially overlapping with the basal-like subtype (1) and frequently occurring in women with germline deleterious BRCA1 mutations (2–5). Most population-based studies report a TNBC prevalence of 10% to 20%, but higher values can be found in some ethnic groups (5–9). While often presenting in premenopausal age, TNBCs also appear as interval cancers in population-based mammography screening programs (10). Frequent phenotype features of TNBCs in the general female population are high

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).


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Translational Relevance

Although multimodal screening programs allow for an earlier detection of breast cancer in asymptomatic women at high genetic-familial risk, scarce information is available on the outcome of these patients when affected with a triple-negative breast cancer (TNBC), i.e., a cancer testing negative to estrogen and progesterone receptors in the absence of HER2 overexpression. Population-based studies showed that, compared with other breast cancer phenotypes (non-TNBCs), TNBCs have a more aggressive clinical course, a less favorable pattern of recurrence, and higher 5-year mortality rate. The current analysis of data from the HIBCRIT-1 study, annual screening sessions including mammography, ultrasonography, and magnetic resonance imaging (MRI), and follow-up until June 2015 showed that the significant differences commonly reported for the overall and disease-free survival rates between TNBC and non-TNBC subsets could be drastically reduced in high-risk women, as an effect of the combination of a multimodal MRI-including screening and adequate treatment protocols.

tumor grade (G3), large tumor size (pT2–pT3), weak relationship between tumor size and nodal status, and poor clinical outcome (5–7, 11, 12).

Recurrence and survival analyses reported in 2007 by Dent and colleagues (11) for a hospital-based cohort of 1,601 women diagnosed with primary breast cancer (Toronto, 1987–1997) showed for the TNBC subset a rapid rise in the risk of recurrence, with a peak at 1 to 3 years after diagnosis, a distant recurrence rarely preceded by local recurrence, a rapid progression from distant recurrence to death and increased mortality rate within 5 years. A significantly shorter 10-year overall survival rate (73%) was also reported by the Breast Cancer Group Trials VIII and IX for TNBCs compared with hormone receptor–positive patients with either low or high proliferative activity (survival rates 89% and 83%, respectively) in a cohort of 1,951 early-stage node-negative breast cancers diagnosed from 1988 to 1999 (12).

Scarcce knowledge is currently available on outcome of patients found affected with TNBC during intensive screening of women at high genetic-familial risk of breast cancer, i.e., women found to be carriers of deleterious \textit{BRCA1} or \textit{BRCA2} mutations or women at high risk as defined on the only basis of a strong family history (SFH) of breast cancer and/or ovarian cancer. An elevated percentage of TNBCs and reduced survival rates are expected for high-risk women, mainly in view of the high susceptibility of \textit{BRCA1} mutation carriers to develop cancers of the aggressive basal-like phenotype, frequently associated with hormone receptor negativity, and lack of HER2 overexpression (13–16). In this context, a number of studies demonstrated the capability of annual multimodal screening programs including magnetic resonance imaging (MRI) to provide an earlier diagnosis of breast cancer in asymptomatic high-risk women (17–25), leading to expectations for a possible improvement in the outcome of screened high-risk women who are diagnosed with breast cancer. As a consequence, phenotype characteristics, patterns of recurrence, and survival of screened high-risk women affected with TNBC deserves attention, also for the sake of optimizing evidence-based recommendations to be offered to these patients.

For these reasons, we analyzed phenotype features and survival rates of TNBC and non-TNBC patients diagnosed during the HIBCRIT-1 prospective MRI-including screening study on women at high genetic/familial breast cancer risk, coordinated by the Istituto Superiore di Sanità (Rome, Italy) in eighteen Italian centers from June 2000 to March 2008 (17, 18), including data on follow-up until June 2015 (see Notes). The results of these analyses were then compared with those reported for TNBC and non-TNBC cases diagnosed in a hospital-based cohort of unscreened women of the general population (11).

Materials and Methods

Patients

We analyzed the HIBCRIT-1 database (18) collected on a cohort of 501 asymptomatic high-risk women including either proven \textit{BRCA1} (n = 184) or \textit{BRCA2} mutation carriers (n = 146), first-degree relatives of \textit{BRCA1} or \textit{BRCA2} mutation carriers (n = 12), or women with SFH of breast cancer or ovarian cancer (n = 159). Genetic tests for identifying \textit{BRCA} mutation carriers and criteria for SFH classification were previously described (17, 18). High-risk women without \textit{BRCA1}/\textit{BRCA2} deleterious mutations or with variants of unknown significance, but a SFH, were included in the SFH subgroup. The database included the results of a total of 1,592 screening sessions. Overall, 52 women were found affected with a breast cancer (incidence per year-woman 3.3%), 44 of them (85%) with an invasive cancer, 8 (15%) with a ductal carcinoma \textit{in situ}. Patients affected with invasive cancer were 20 \textit{BRCA1} and 9 \textit{BRCA2} mutation carriers, while 15 patients were classified as SFH (18).

In the current study, patients diagnosed with an invasive breast cancer were divided into the TNBC and non-TNBC subsets. In a complementary database we reported, for each patient, demographics, breast cancer risk class, previous breast cancer events, phenotype characteristics of the breast cancer event detected during the HIBCRIT-1 study (histopathologic type, tumor grade, tumor size, and nodal involvement), adopted treatment (breast conserving surgery, therapeutic mastectomy, chemotherapy, radiotherapy, endocrine therapy), possible contralateral prophylactic mastectomy, additional breast cancer-related events during the follow-up (ipsilateral and contralateral relapses, axillary metastasis, and metastatic spread), and status of the patient at the latest reported follow-up date. In the case of multilocal or multicentric cancer, the largest lesion was considered for \textit{pT} classification; for bilateral cancers, the side with the largest tumor size was considered for defining the patient hormonal receptor status and other prognostic factors.

Multimodal imaging and reference standard

Mammography, ultrasonography (US), and dynamic contrast-enhanced MRI examinations were categorized according to the Breast Imaging Reporting and Data System (BI-RADS; ref. 26). BI-RADS 1, 2, and 3 findings were considered as negative results, BI-RADS 4 or 5 as positive results. Of 52 true positive findings, 44 were pathologically proven at surgery as invasive cancers. Technical details of mammography, US, and MRI were already...
described (17, 18); a summary of the MRI protocol is provided in
the legend of Fig. 1.

Immunohistochemistry
Data on ER and PR status obtained using immunohistochemical
analysis of surgical tumor specimens were reported by each
participating institution. The cutoff for ER or PR positivity was
>10% positive tumor cells with nuclear staining (11). The HER2
positivity was defined as scored 3+ by immunohistochemistry or
2+ by immunohistochemistry and positivity to HER2 gene ampli-
fication by FISH (27).

Treatment
Therapeutic protocols were independently decided by each
Centre according to standard clinical regimens, and in agreement
with national and international guidelines.

Follow-up
Data on clinical course after diagnosis were available for all 44
patients affected with an invasive breast cancer (41 screen-
detected and 3 interval). One interval cancer was detected in a
woman who withdrew from the study and was diagnosed else-
where 6 months after her last screening session, but all relevant
information was provided to the database.

The follow-up started at breast cancer diagnosis during the
HIBCRIT-1 study (June 2000–March 2008) and ended on June
2015. The median follow-up time was 9.7 years [longest follow-
up time 13.7 years from diagnosis; 89% (39/44) ≥ 5 years; 53%
(23/44) ≥ 9 years].

Statistical analysis
Differences between TNBC and non-TNBC patients were eval-
uated using the Mann–Whitney U test for continuous variables
and \( \chi^2 \) or Fisher exact test, whenever applicable, for categorical
variables. Differences in sensitivity of imaging modalities were
evaluated using the Cochrane Q test and McNemar test for post hoc
analysis. P values <0.05 were considered as significant.

Overall survival was assessed from diagnosis to breast cancer-
related death or to the latest available follow-up date. Disease-
free survival was evaluated from diagnosis to the first reported
evidence of clinically or imaging-proven metastatic disease, or
ipsilateral, contralateral, or axillary recurrence. Kaplan–Meier
survival curves were obtained for patients affected with either a
TNBC or a non-TNBC and log-rank tests were used to evaluate
the significance of differences between the two subsets (SPSS
Statistics, IBM Corporation).

Comparison with a previous large registry
The tumor phenotype characteristics and survival rates of high-
risk women who had triple negative or other forms of breast cancer
during the HIBCRIT-1 study were compared with those retrospec-
tively reported for a large hospital-based registry of unscreened
women of the general population, affected with primary breast
cancer (Women's College Hospital, Toronto; ref. 11).

Results
Clinical features and \textit{a priori} risk stratification
Out of the 44 patients diagnosed with an invasive breast cancer,
14 (32%) had a TNBC and 30 (68%) a non-TNBC. In the TNBC

Figure 1.
A 55-year-old \textit{BRCA1} mutation carrier, already treated for an invasive ductal cancer of the left breast at 33 years of age, underwent multimodal screening
including clinical breast examination (CBE), mammography, US, and MRI. The left breast only showed minimal signs of the previous treatment at each screening
modality. Mammography of the right breast showed a negative dense breast (A and B). Also CBE and US (not shown) were negative. At MRI, in the central
region of the right breast, the unenhanced T2-weighted axial short-tau inversion recovery sequence (C) showed a small hyperintense mass, confirmed at the
subtracted (contrast-enhanced minus unenhanced T1-weighted gradient echo) coronal image (D). At pathology, an invasive ductal carcinoma 6 mm in
diameter was diagnosed. Sentinel node biopsy was negative. The MRI protocol for the HIBCRIT-1 study comprised at least a T2-weighted sequence (fast/turbo
spin-echo with or without fat saturation, or a short tau inversion recovery) and a dynamic contrast-enhanced T1-weighted spoiled gradient-echo sequence,
before and after 0.1 mmol/kg of a 2-compartment extracellular gadolinium-chelate. For more details on the MRI protocol, see refs. 17 and 18.
subset, ER status was 0 or <1% in 13 of 14 and 1% to 10% in 1 of 14 patients; PR status was <1% in 12 of 14 and 1% to 10% in 2 of 14; and the HER2 score was 0 in 12 of 14 and 1 in 2 of 14 patients. Two patients diagnosed with bilateral breast cancer had a non-TNBC on both sides. No patients had distant metastasis at the time of diagnosis.

Demographics, a priori risk stratification, and previous history of breast cancer events reported for patients diagnosed with TNBC or non-TNBCs are compared in Table 1. No significant differences were found between the two subgroups for age at diagnosis, percentage of patients diagnosed under the age of 50 years, percentage of patients in menopausal status, percentage of patients who underwent prophylactic oophorectomy or chemically induced menopause before enrollment, percentage of patients who had a previous breast cancer, and age of onset of the previous breast cancer. Significant differences were instead found in the distribution of risk classes between the TNBC and non-TNBC subsets (Table 1). In particular, the percentage of BRCA1 mutation carriers was as high as 79% (11/14) in TNBCs compared with 30% (9/30) in non-TNBCs (P < 0.001), while the percentage of SFH patients was higher in non-TNBCs (47%, 14/30) than in TNBCs (7%, 1/14). Notably, 55% (11/20) of BRCA1 mutation carriers had a TNBC, while 93% (14/15) of SFH patients had a non-TNBC.

Sensitivity of screening modalities

In the detection of invasive breast cancers, the sensitivity of MRI (90%) outperformed that of mammography (43%, P < 0.001), US (61%, P = 0.004), and combination of mammography and US (66%, P = 0.031; Supplementary Table S1).

Focusing on small (pT1a plus pT1b) invasive breast cancers, MRI sensitivity was 93% (14/15) to be compared with 35% (6/17) for mammography (P = 0.008) and 50% (8/16) for US (P = 0.031).

When comparing the sensitivity of different modalities in detecting TNBCs or non-TNBCs (Supplementary Table S1), no significant differences were found for mammography (43% in both subsets) and US (57% versus 62%, P = 1.000), while a borderline significant difference was found for MRI which detected only 75% of TNBCs and 96% of non-TNBCs (P = 0.078). Cancers detected by MRI only accounted for 71% of TNBCs and 23% of non-TNBCs (P = 0.006). One example of MRI-only detection of a small invasive breast cancer is presented in Fig. 1. Each of the three interval cancers was a TNBC in a BRCA1 mutation carrier.

Histopathology

As shown in Table 2, significant differences were found between TNBCs and non-TNBCs: invasive ductal carcinomas (IDC) were 86% of TNBCs and 43% of non-TNBCs (P = 0.010); G3 IDCs accounted for 71% of TNBCs and 23% of non-TNBCs (P = 0.006); the mean tumor size of TNBCs was larger than that of non-TNBCs, but below 2 cm in both subsets (16 ± 5 mm vs. 12 ± 6 mm, P = 0.007). A borderline significant difference was found for nodal negativity: 92% of TNBCs versus 65% of non-TNBCs. Furthermore, 80% (8/10) of G3 IDC-TNBC patients had negative nodal status, irrespective of tumor size, variable from 10 to 25 mm.

Treatment

The treatment protocols adopted during the study are summarized in Table 2. No patient received neoadjuvant chemotherapy. During the study, breast conserving surgery was more frequently performed at diagnosis in the non-TNBC subset (57%) than in the TNBC subset (21%), with borderline significance (P = 0.050), while contralateral prophylactic mastectomy was significantly more frequent in TNBC patients (43%, 6/14) than in non-TNBC patients (10%, 3/30, P = 0.019).

Adjuvant chemotherapy was administered to 100% (13/13) TNBCs for whom this information was reported, compared with 44% (12/27) non-TNBCs (P < 0.001). Conventional anti-ER therapy was reported for all 19 ER-positive non-TNBC patients, while trastuzumab was administered to only one of the 14 HER2-positive patients.

Outcome

The median follow-up time was 9.7 years overall, 9.0 years for TNBCs (longest follow-up time 12.0 years after diagnosis; 86% (12/14) ≥ 5 years; 50% (7/14) ≥ 9 years) and 9.8 years for non-TNBCs (longest follow-up time 13.7 years; 93% (28/30) ≥ 5 years; 53% (16/30) ≥ 9 years) without significant difference between the two subsets (P = 0.668). During follow-up, metastatic spread and death occurred for 14% (6/44) of all patients; 14% (2/14) of

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>TNBC (n = 14)</th>
<th>Non-TNBC (n = 30)</th>
<th>P</th>
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</thead>
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<tr>
<td>Risk categories</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>BRCA1 mutation carriers (n = 20)</td>
<td>79% (11/14)</td>
<td>30% (9/30)</td>
<td>0.008</td>
</tr>
<tr>
<td>BRCA2 mutation carriers (n = 9)</td>
<td>14% (2/14)</td>
<td>25% (7/30)</td>
<td>0.004</td>
</tr>
<tr>
<td>Strong family history (n = 15)*</td>
<td>7% (1/14)</td>
<td>47% (14/30)</td>
<td>0.695</td>
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<tr>
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<tr>
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<tr>
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<td>35–72</td>
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<tr>
<td>Diagnosed under 50 years</td>
<td></td>
<td></td>
<td>0.325</td>
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<tr>
<td>Median</td>
<td>50% (7/14)</td>
<td>45% (13/30)</td>
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<td>Diagnosed in menopausal status</td>
<td>64% (9/14)</td>
<td>62% (18/29)*</td>
<td></td>
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<tr>
<td>Median</td>
<td>43% (6/14)</td>
<td>27% (8/30)</td>
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</tr>
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<td>Age at previous breast cancer, years</td>
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<td>47% (14/30)</td>
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<td>Median</td>
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<tr>
<td>Range</td>
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<td>31–65</td>
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</table>

NOTE: P values were calculated using Mann–Whitney U test for age at diagnosis during the study and age at previous breast cancer, and Fisher exact test for all remaining comparisons.

*Including 5 gene-tested patients with a strong family history of breast cancer without any BRCA1/2 deleterious mutations or with variants of unknown significance.

1One not reported.

1One not reported.
TNBCs and 13% (4/30) of non-TNBCs. A detailed description of patients who died from metastatic breast cancer disease in the two subsets is reported in Table 3. No patients died of other diseases or casualties. The 12 TNBC survivors were reported to be alive with no evidence of disease (NED) at their respective latest follow-up date (from 7.5 to 12.0 years from diagnosis). Twenty-five non-TNBC survivors were reported to be alive NED at the latest follow-up date (from 6.1 to 13.7 years) while one non-TNBC patient was lost from follow-up at about 6 months, after bilateral mastectomy.

The three TNBCs detected as interval cancers during the study were all alive NED at their latest follow-up date (8.0–12.0 years). Details are reported in Supplementary Table S2.

The Kaplan–Meier curves for the overall survival of TNBC and non-TNBC patients are shown in Fig. 2A. The 5-year overall survival rate was 86% ± 9% (mean ± SE) for TNBCs and 93% ± 5% for non-TNBCs, without significant difference (P = 0.946, log-rank test). Moreover, it was 91% ± 4% for the overall cohort of 44 patients, 89% ± 7% for the 20 patients with a proven BRCA1 mutation, and 93% ± 6% for the 15 SFH patients, without significant difference between these two subgroups (P = 0.866). For the 9 patients with a proven BRCA2 mutation, the 5-year overall survival rate was 89% ± 11%.

The patterns of breast cancer recurrence reported for TNBC and non-TNBC patients are shown in Supplementary Table S3. In the TNBC subset, there were two locoregional relapses (one ipsilateral...
at 3.9 years from diagnosis and one axillary metastasis at 1.8 years). Among non-TNBCs, there were eleven locoregional relapses: three ipsilateral (at 0.4, 8.0 and 9.5 years); one axillary metastasis (at 2.8 years); and seven contralateral (at 1.1, 3.6, 4.6, 6.6, 7.1, 8.0 and 8.3 years); patients who had only locoregional relapses were alive NED at the latest follow-up date (from 8.2 to 13.7 years).

Kaplan–Meier curves for disease-free survival are shown in Fig. 2B. The 5-year disease-free survival rate was 77% ± 12% for TNBC and 76% ± 8% for non-TNBC patients, with no significant difference between the two subsets (P = 0.216 log-rank test), while that of patients with proven BRCA1 mutation was 73% ± 10%.

Phenotype features and survival rates of TNBC and non-TNBC patients in the HIBCRIT-1 study are compared in Table 4 with those reported by Dent and colleagues (11) for a hospital-based cohort of unscreened women of the general population, whose breast cancers were diagnosed with conventional modalities from 1987 to 1997.

Discussion

Outcome and recurrence patterns of TNBC patients in the general female population are currently reported to be less favorable than those of non-TNBC patients, with a survival rate as low as that of HER2-positive patients in the pre-trastuzumab era (12). Early tumor detection and the evolution to more aggressive behavior is well known (4, 31, 32). Third, the earlier breast cancer diagnosis allowed by the adjunct of MRI to conventional screening modalities (17–25) could in principle improve life expectancy and morbidity of screen-detected breast cancers. In fact, the adjunct of MRI to mammography into annual screening programs dedicated to high-risk women increased sensitivity from 29% to 50% to 77% to 100%, decreased the interval cancer rate from 35% to 50% to 0% to 12%, and reduced nodal involvement from 20% to 56% to 13% to 31% (33, 34).

Indeed, the impact of multimodal MRI-including screening protocols on patient outcome of high-risk women is under consideration (24, 35, 36). Furthermore, multimodal imaging to screen high-risk women can currently exploit the imaging phenotypes of familial breast cancer (37), with peculiar MRI characteristics of TNBCs (38, 39).

The analysis of data reported here, collected during the HIBCRIT-1 study (18), shows that the MRI sensitivity outperformed that of mammography and US in the detection of both TNBCs and non-TNBCs.

Of note, in their retrospective analysis of a hospital-based cohort of unscreened patients of the general population affected with primary breast cancers detected with conventional modalities, Dent and colleagues (11) showed that, compared with non-TNBCs, TNBCs (11%) had a significantly lower mean age at diagnosis (53 vs. 58 years), higher G3 rate (66% vs. 28%), and larger tumor size (30 vs. 21 mm). Despite the difference in patient cohort size, relevant differences can be appreciated in the HIBCRIT-1 when compared with the Toronto study (see Table 4): (i) a 3-fold higher percentage of TNBCs (32%, 95% CI, 18%–36% vs. 11%, 95% CI, 10%–13%), as expected for a cohort enriched in BRCA1 mutation carriers; (ii) a median age at diagnosis not significantly different in the TNBC and non-TNBC subsets (49 vs. 52 years, P = 0.325), in agreement with the selection of high-risk women; (iii) higher percentages, in non-TNBCs, of ER negativity (37%, 95% CI, 20%–54% vs. 13%, 95% CI, 12%–15%) and HER2 positivity (47%, 95% CI, 29%–65% vs. 16%, 95% CI, 14%–19%), both features being typically associated with higher tumor aggressiveness. Furthermore, when compared with non-TNBCs, our TNBCs showed a significantly higher percentage of grade 3 IDCs (71% versus 23%, P = 0.006) and of grade 3 tumors in general (86% vs. 53%, P = 0.049), in agreement with the higher level of tumor aggressiveness usually associated with triple negativity. The generally higher levels of tumor aggressiveness for breast cancers detected in our cohort of high-risk women are further supported by the higher rates of grade 3 tumors in the
Table 3. HIBCRIT-1 patients who were diagnosed with a TNBC or a non-TNBC and died from breast cancer during the follow-up

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<td>Grade</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>2</td>
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</tr>
<tr>
<td>Estrogen receptor (%)</td>
<td>0</td>
<td>0</td>
<td>95</td>
<td>0</td>
<td>Right 90%; left 0%</td>
<td>66–100</td>
<td></td>
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</tr>
<tr>
<td>Progesterone receptor (%)</td>
<td>0</td>
<td>0</td>
<td>20</td>
<td>33–67</td>
<td>Right 0%; left 60%</td>
<td>0–1</td>
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<tr>
<td>HER2 (score)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Right 0%; left 0%</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Lymph node status</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
<td></td>
<td>Negative</td>
<td>Right negative; left previous dissection</td>
<td>Negative</td>
<td></td>
<td></td>
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<tr>
<td>Treatment</td>
<td>Mastectomy</td>
<td>Mastectomy</td>
<td>Conserving</td>
<td>Mastectomy</td>
<td>Bilat. mastectomy</td>
<td>Conserving</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast radiotherapy</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine therapy</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years from HIBCRIT-1 diagnosis to death</td>
<td>4.5</td>
<td>3.0</td>
<td>4.9</td>
<td>5.7</td>
<td>15</td>
<td>9.8</td>
<td></td>
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</tbody>
</table>

Notes:
- *Previous breast cancer at 37 years; mother, breast cancer at 52, deceased at 54 years; maternal aunt, breast cancer at 47, deceased at 52 years.
- **Sister, breast cancer at 44, 51, and 61 years (BRCAX); mother, breast cancer at 64 years; mother’s brother, breast cancer at 60 years.
- **Previous breast cancer events in 4 of these 6 women should be considered as a potential confounding factor, even though in 2 of them a different histotype was diagnosed during the study.
- **Pharmacological menopause after a previous breast cancer event.
- **Cyclophosphamide/methotrexate/5-fluorouracil × 6.
- **Doxorubicin × 4 + cyclophosphamide/methotrexate/5-fluorouracil × 4.
- **Paclitaxel weekly for about 4 months.
- **Tamoxifen (patient # 16); anastrozole (patient # 20); letrozole, enantone (patient # 27); exemestane, letrozole (patient # 34).

HIBCRIT-1 versus the Toronto study, for both the TNBC (86% vs. 66%) and the non-TNBC patient subsets (53% versus 28%).

Despite the generally more aggressive phenotypes of breast cancers in our study, we had a 45% reduction in the mean tumor size for both the TNBC or non-TNBC subsets, compared with those of the Toronto study (with decreases from 30 to 16 mm and from 21 to 12 mm, respectively). Interestingly, the mean tumor size of all invasive breast cancers in HIBCRIT-1 was 13 mm, the same value recently reported by Evans and colleagues (36) for the UK MRI-including screening of high-risk women. The higher mean tumor size of TNBCs versus non-TNBCs can be attributed to the higher aggressiveness and growth rate of the former subset. The higher sensitivity of MRI in detecting small breast cancers likely strongly contributed to the pT downstaging of breast cancers detected in both subgroups. As the percentage of MRI-only detected cancers was similar for TNBCs (25%) and non-TNBCs (31%), the potential benefits from MRI were evenly distributed over the two breast cancer subsets.

Lymph node negativity for all invasive breast cancers was 72% in the HIBCRIT-1 study compared with a range from 69% to 87% reported by eight different high-risk screening studies (34). Notably, in HIBCRIT-1, there was a trend toward higher lymph node negativity for TNBCs (92%) than for non-TNBCs (65%), in spite of the larger mean tumor size of the former subset. This feature is in general agreement with the reported disruption of the positive correlation between breast tumor size and nodal status in BRCA1-related breast cancers (40). The larger tumor size of TNBCs was instead associated, as usual, with higher average lymph node positivity in this subset when compared with the non-TNBC subset in the Toronto study on patients of the general population (Table 4).

Importantly, we found a nonsignificantly different 5-year overall survival rate for TNBC (86 ± 9%) compared with non-TNBC patients (93 ± 5%), in spite of the more aggressive features of the former subset, differently from the Toronto study in which the 5-year TNBCs survival was about 70% (11). This improved survival rate of TNBCs, similar to that of non-TNBCs, may derive from multiple factors such as: (i) the beneficial effect of an earlier tumor detection; (ii) the higher sensitivity of BRCA1-associated tumors to chemotherapy, due...
However, the 5-year disease-free survival rate of both subsets did not differ significantly from the Toronto study, in which the risk of recurrence was significantly higher for TNBC compared with non-TNBC patients, again differently from the comparison between a hospital-based unscreened cohort of patients diagnosed with conventional modalities and the cohort of patients diagnosed during the HIBCR1-T MRI-including screening program conducted in Norway from 2000 to 2008; ref. 18 and current work.

A debate is open about the impact of MRI-including screening protocols on the survival of BRCA1 mutation carriers found affected with breast cancer (24, 35, 36, 42, 43). Notably, a substantial progress took place in the last two decades in the survival of BRCA1 mutation carriers. A 5-year overall survival as low as 50% was reported for them (compared with about 90% for noncarriers) in a historical cohort of women affected with node-negative breast cancers from 1986 to 1995 (44). An improved survival of 75% (95% CI, 56%–86%) has been recently reported by Møller and colleagues (35) for a cohort of 63 BRCA1 mutation carriers found affected with invasive breast cancer during an MRI-including surveillance program conducted in Norway from 2001 to 2011. Our data, collected within a very similar time window, not only confirmed the similar phenotype features of TNBC and BRCA1-associated breast cancers, but also showed a further improvement in the 5-year overall survival rate of BRCA1-mutated patients up to 89% ± 7%. As reported in Table 4, our BRCA1-mutated patients had clinical and phenotype features similar to those reported in the Norway study (35) in terms of age at diagnosis (about 49 years), tumor size (13–14 mm), as well as percentages of ER-negative tumors (76%–80%), G3 tumors (68%–75%), and nodal negativity (80%–90%). A reason for our higher 5-year overall survival may have been the higher rate of adjuvant chemotherapy administered to our BRCA1-mutated patients (89% vs. 65%), in agreement with recent reports (45, 46). An assessment of the additional impact of therapeutic and contralateral prophylactic mastectomies on the survival of MRI-screened BRCA1 mutation carriers warrants further investigations.

<table>
<thead>
<tr>
<th>Table 4. Triple-negative breast cancer (TNBC) versus non-TNBC patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospital-based unscreened cohort of primary breast cancer patients (Toronto, 1987–1997; ref. 11)</strong></td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td><strong>P</strong></td>
</tr>
<tr>
<td>Mean age at diagnosis, years</td>
</tr>
<tr>
<td>ER negative</td>
</tr>
<tr>
<td>PR negative</td>
</tr>
<tr>
<td>HER2 positive</td>
</tr>
<tr>
<td>Tumor size (mean, mm)</td>
</tr>
<tr>
<td>Grade 3</td>
</tr>
<tr>
<td>Negative lymph node status</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Missing</td>
</tr>
<tr>
<td>Follow-up (years)</td>
</tr>
<tr>
<td>Breast cancer–specific death</td>
</tr>
<tr>
<td>Time to death (median, years)</td>
</tr>
<tr>
<td>5-year overall survival</td>
</tr>
<tr>
<td>Risk of distant recurrence for TNBC vs. non-TNBC HR 2.6 (2.0–3.5)</td>
</tr>
<tr>
<td>Risk of local recurrence for TNBC vs. non-TNBC HR 1.5 (1.0–2.5)</td>
</tr>
</tbody>
</table>

**Abbreviation:** NC, not calculated.

aEleven TNBCs and nine non-TNBCs.

bSample size too small for statistical comparison.

cCox model.

dLog-rank test.

NOTE: Comparison between a hospital-based unscreened cohort of patients diagnosed with conventional modalities and the cohort of patients diagnosed during the HIBCR1-T MRI-including screening program conducted in Norway from 2000 to 2008; ref. 18 and current work.

A debate is open about the impact of MRI-including screening protocols on the survival of BRCA1 mutation carriers found affected with breast cancer (24, 35, 36, 42, 43). Notably, a substantial progress took place in the last two decades in the survival of BRCA1 mutation carriers. A 5-year overall survival as low as 50% was reported for them (compared with about 90% for noncarriers) in a historical cohort of women affected with node-negative breast cancers from 1986 to 1995 (44). An improved survival of 75% (95% CI, 56%–86%) has been recently reported by Møller and colleagues (35) for a cohort of 63 BRCA1 mutation carriers found affected with invasive breast cancer during an MRI-including surveillance program conducted in Norway from 2001 to 2011. Our data, collected within a very similar time window, not only confirmed the similar phenotype features of TNBC and BRCA1-associated breast cancers, but also showed a further improvement in the 5-year overall survival rate of BRCA1-mutated patients up to 89% ± 7%. As reported in Table 4, our BRCA1-mutated patients had clinical and phenotype features similar to those reported in the Norway study (35) in terms of age at diagnosis (about 49 years), tumor size (13–14 mm), as well as percentages of ER-negative tumors (76%–80%), G3 tumors (68%–75%), and nodal negativity (80%–90%). A reason for our higher 5-year overall survival may have been the higher rate of adjuvant chemotherapy administered to our BRCA1-mutated patients (89% vs. 65%), in agreement with recent reports (45, 46). An assessment of the additional impact of therapeutic and contralateral prophylactic mastectomies on the survival of MRI-screened BRCA1 mutation carriers warrants further investigations.
This study has limitations. First, even though the number of screened women and of diagnostic sessions were large (501 and 1,592, respectively), the sample size of the two breast cancer subsets here analyzed was relatively small, potentially explaining some cases of borderline statistical significance. It appears however worth emphasizing that this size was obtained through the coordinated efforts of 18 centers, in a time window of about eight years (plus over 9 years follow-up). In spite of the relatively small number of TNBCs and non-TNBCs cases, we reached a statistical significance in the comparison between these two subsets in terms of prognostic factors, mean tumor size, and treatment options. We believe that reaching a substantially higher number of TNBCs in any single prospective screening study is not easy. A meta-analysis of different studies, possibly based on individual patient outcome data, might better investigate survival rates of high-risk women found affected with breast cancer during an MRI-including screening. Second, the tumor pathologic characteristics were not submitted to a central pathologic review. However, all pathologists locally involved in the centers had at least twenty years of experience with breast pathology. Third, the sample size did not allow us to explore further details on the genotype and phenotype features of the inherently heterogeneous TNBC subset. Finally, as already mentioned, we were not able to distinguish between the effect on survival of an early diagnosis mainly due to MRI and the effects of a better treatment, even though we should consider that relevant ethical concerns prevent the possibility of randomized controlled trials exploring this issue.

In conclusion, combining an MRI-including screening with updated therapy protocols, the commonly reported gap in outcome between TNBC and non-TNBC patients can be reduced in high-risk women. Cooperative efforts devoted to a joint accrual of larger datasets and integrated analyses of long-term follow-up data collected from different prospective studies on high-risk women are warranted to enhance the clinical impact of our study.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References

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Conception and design: F. Podo, F. Sardanelli
Development of methodology: F. Podo, F. Sardanelli
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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): F. Podo, F. Santoro, G. Di Leo, F. Sardanelli
Writing, review, and/or revision of the manuscript: F. Podo, F. Santoro, G. Di Leo, S. Manoukian, C. de Giacomoni, L. Cortesi, R.M. Trimboli, L. Preda, B. Bonanni, L. Martincich, A. Savarese, A. ConteGiaccomo, F. Sardanelli
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): F. Podo, F. Santoro, S. Manoukian
Study supervision: F. Podo, F. Santoro, F. Sardanelli

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Triple-Negative versus Non–Triple-Negative Breast Cancers in High-Risk Women: Phenotype Features and Survival from the HIBCRIT-1 MRI-Including Screening Study

Franca Podo, Filippo Santoro, Giovanni Di Leo, et al.


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