

ARTICLE



Epidemiology

Clinicopathological features and *BRCA1* and *BRCA2* mutation status in a prospective cohort of young women with breast cancer

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BACKGROUND: Breast cancer in young women is more likely to have higher risk features and be associated with germline *BRCA1/BRCA2* mutations. We present the clinicopathologic features of breast cancers in a prospective cohort of young women, and associations between surrogate molecular subtype and *BRCA1/BRCA2* mutation status.

METHODS: Histopathological features, biomarker status, tumour stage and *BRCA* status were collected. Invasive tumours were categorised as luminal A-like (ER + and/or PR +, HER2−, grade 1/2), luminal B-like (ER + and/or PR +, HER2 +, or ER + and/or PR +, HER2−, and grade 3), HER2-enriched (ER/PR−, HER2 +) or triple-negative.

RESULTS: In all, 57.3% (654/1143) of invasive tumours were high grade. In total, 32.9% were luminal A-like, 42.4% luminal B-like, 8.3% HER2-enriched, and 16.4% triple-negative. Among different age groups, there were no differences in molecular phenotype, stage, grade or histopathology. 11% (131) of tumours were from *BRCA* mutation carriers; 64.1% *BRCA1* (63.1% triple-negative), and 35.9% *BRCA2* (55.3% luminal B-like).

DISCUSSION: The opportunity to provide comparisons across young age groups, *BRCA* mutation status, surrogate molecular phenotype, and the identification of more aggressive hormone receptor-positive phenotypes in this population provides direction for future work to further understand and improve disparate outcomes for young women with luminal B-like cancers, particularly *BRCA2*-associated cancers, with potential implications for tailored prevention and treatment.

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BACKGROUND

Breast cancer is the most common cancer type diagnosed among young women (age ≤ 40 years) worldwide and has the highest cancer-related death rate in this age group [1]. Of note, an increased incidence of breast cancer in young women has been seen recently, largely driven by an increase in hormone receptor-positive tumours [2, 3]. Breast cancer arising in this age group is more likely to have more aggressive features than in older women, with a greater proportion of Stage III, high-grade hormone receptor-positive, and hormone receptor-negative tumours in young women [2]. Furthermore, a higher risk of relapse has been shown in women ≤ 40 years when compared to older women, with an inferior relapse-free survival seen among women with oestrogen receptor (ER) positive (+)/human epidermal growth factor 2 receptor (HER2) negative (−) tumours, in particular [4, 5].

Differences in the distribution of the molecular phenotypes by age and race have been demonstrated [6, 7]. Some prior studies have identified a higher proportion of triple-negative and HER2-enriched tumours in young women [4], and among African-American women there is a preponderance of triple-negative breast cancers [8, 9]. In addition, the outcomes by molecular phenotypes vary by age, with a worse prognosis seen in younger women with luminal A-like subtypes and Stage I to III breast cancer compared with older women [5, 10, 11]. Paradoxically, among young women with Stage IV breast cancer, a lower risk of breast cancer-related death has been observed in luminal A-like and luminal B-like subtypes when compared to older women of the same stage [12].

BRCA1 and *BRCA2* mutation carriers are well known to have an increased risk of developing breast cancer, [13–15] and in young women, breast cancer is more likely to be associated with

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germline *BRCA1* or *BRCA2* mutations [16–19]. Studies evaluating the distribution of molecular phenotypes among *BRCA1* or *BRCA2* mutation carriers have documented a higher proportion of triple-negative cancers among *BRCA1* mutation carriers and a higher proportion of luminal B-like cancers among *BRCA2* mutation carriers [20–22]. A low *BRCA* mutation detection rate (6.4%) among luminal-like early-onset breast cancer patients has been described with a greater proportion being *BRCA2* mutation carriers (4.6%), and a lesser proportion being *BRCA1* mutation carriers (1.8%) [23]. Moreover, *BRCA1* status and ER negativity has been associated with higher pathologic complete response (pCR) after neoadjuvant chemotherapy; and better relapse-free survival and overall survival was observed among those who achieved a pCR [24]. However, the distribution of molecular phenotypes in young women according to *BRCA1* or *BRCA2* mutation status is not as well-defined.

We previously reported a higher distribution of luminal B-like and HER2-enriched tumours among young women (≤ 40 years) [25]. Here, we present the clinical and pathologic features of invasive disease in the fully assembled prospective cohort of young women with breast cancer, as well as associations between surrogate molecular phenotype and *BRCA1* and *BRCA2* mutation status.

PATIENTS AND METHODS

Study design and population

The Young Women's Breast Cancer Study (NCT#01468246) is a multi-institutional prospective cohort study of women newly diagnosed with breast cancer at age 40 years and younger enrolled from 2006 to 2016. As has been described previously [25, 26], women were identified through pathology record review complemented by clinic list review at the Dana-Farber Cancer Institute and Brigham and Women's Hospital, as well as nine other participating institutions within Massachusetts and three out of state, and were eligible for enrollment provided they were able to respond to questionnaires in English. Participants responding to an invitation by mail, provided written informed consent authorising medical record review that included data abstraction of patient stage, breast tumour biomarker status (ER, progesterone receptor (PR) and HER2) and *BRCA* mutation status, blood sample and pathology specimen collection, and baseline and follow-up participant questionnaires. Institutional review board (IRB) approval for the study was obtained through the Dana-Farber/Harvard Cancer Centre and other participating centres.

Pathology review

Histopathology slides were reviewed centrally by the study pathologists, including an expert breast pathologist who reviewed all cases (LCC). When available, both the initial core biopsy and subsequent excision or mastectomy specimens were reviewed. Using a standardised case-reporting form, specific histologic features were recorded for each specimen, including histologic grade (Ellston modification of the Bloom-Richardson tumour grade), presence or absence of a central fibrotic focus, zones of geographic necrosis, the pattern of the tumour margins (invasive or pushing/circumscribed) and degree of associated lymphocytic infiltration (none/mild or moderate/marked) [25].

Classification of molecular phenotype

Using the histologic tumour grade from central pathology review and biomarker status (ER, positive or negative; PR, positive or negative; and HER2, positive/amplified or negative/nonamplified) extracted from pathology reports, cases were classified as one of four molecular subtypes. The use of immunohistochemistry as a surrogate for molecular classification by gene expression profiling has been used in a number of large population-based studies [8, 27–30], has been shown to be an acceptable approximate of molecular phenotype [31] and is supported by the St. Gallen International Expert Consensus Statement [32]. As described previously [25], cases that were ER + and/or PR +, HER2-, and either histologic grade 1 or 2 were classified as luminal A-like cancers. Cases that were ER + and/or PR + and HER2 + or ER + and/or PR + and HER2- and that were histologic grade 3 were classified as luminal B-like cancers. Cases that were ER-, PR-, and HER2 + were classified as HER2-enriched. Cases that were negative for

ER, PR and HER2 were classified as triple-negative, the clinicopathologic surrogate of basal-like carcinoma [32]. HER2 was considered positive if immunohistochemical stains were reported as 3+ and/or if HER2 fluorescence in situ hybridisation (FISH) showed gene amplification per ASCO/CAP definitions at the time of diagnosis.

BRCA status

BRCA mutation status was retrieved by medical record review or patient survey if not in the medical record. *BRCA* status was recorded as the deleterious mutation in *BRCA1* or *BRCA2*, no mutation detected (wild-type, including variants of uncertain significance [VUS]), or unknown.

Statistical analyses

Statistical analyses were carried out with SAS 9.4 (SAS + Institute, Cary, NC). Pearson Chi-squared statistics were calculated to assess the difference among three age groups (≤ 30 , 31–35 and 36–40 years) of young breast cancer patients' tumours with respect to the surrogate molecular phenotype of invasive carcinomas, pathological features, and *BRCA* mutation status.

RESULTS

With the recruitment period finalised, pathology review has been completed on all 1297 eligible participants (Fig. 1) (5 of the 1302

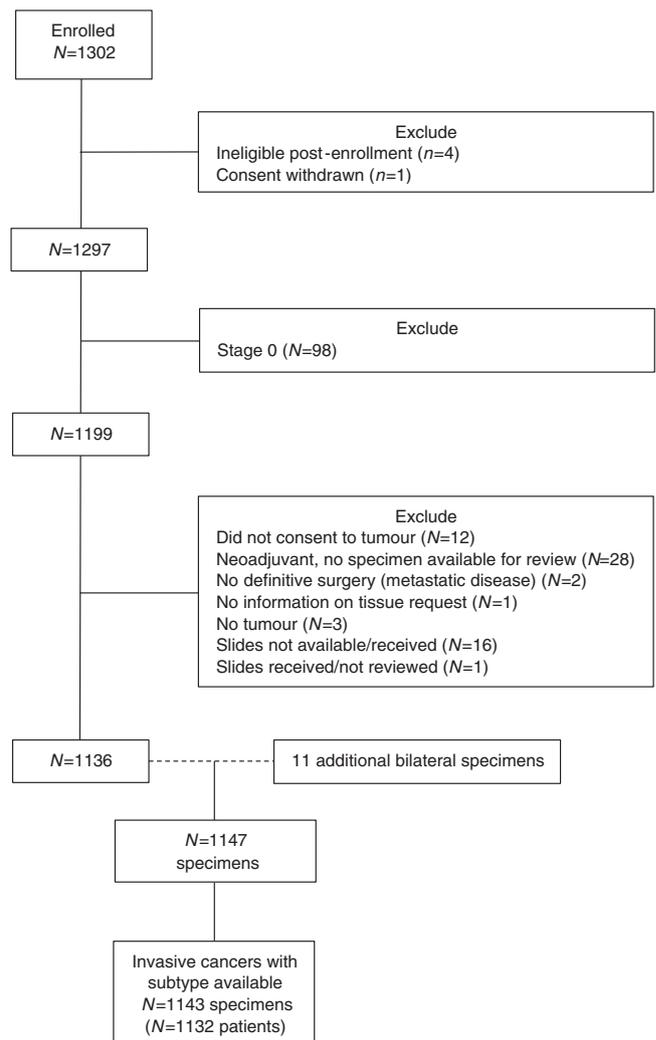


Fig. 1 Profile of study population. This diagram provides an outline of patients enrolled in the study, those excluded due to ineligibility, those excluded from this analysis due to Stage 0 status, and those with insufficient material for evaluation.

Table 1. Patient characteristics for entire study population.

Total patients	N = 1297
Median age at diagnosis (years, range)	37 (17–40)
	N (%)
Race*	
American Indian or Alaskan native	6 (0.5)
Asian	88 (6.8)
Black, Haitian or African American	48 (3.7)
White	1101 (84.9)
Other/unknown	38 (2.9)
Multiracial	16 (1.2)
First-degree family history breast or ovarian cancer**	
Yes	176 (15.8)
No	936 (84.0)
Unsure	2 (0.2)
Missing	183
Bilateral	
Yes	21 (1.6)
No	1276 (98.4)
Stage	
0	98 (7.6)
I	413 (31.8)
II	525 (40.5)
III	197 (15.2)
IV	64 (4.9)
Tumour grade	
Grades 1 and 2	534 (41.2)
Grade 3	752 (58.0)
Missing	11 (0.9)
Oestrogen receptor (ER)	
Positive	945 (72.9)
Negative	351 (27.1)
Missing	1 (0.1)
Progesterone receptor (PR)	
Positive	848 (65.4)
Negative	441 (34.0)
Missing	8 (0.6)
HER2 (any ER status)	
Positive	360 (27.8)
Negative	880 (67.9)
Missing/not performed***	57 (4.4)
Subtype	
Luminal A-like (ER and/or PR +, HER2–, grade 1 or 2)	395 (30.5)
Luminal B-like (ER and/or PR +, HER2–, grade 3)	269 (20.7)
Luminal B/HER2 (ER and/or PR +, HER2 +)	255 (19.7)
HER2-enriched (ER–, PR–, HER2 +)	105 (8.1)
Triple-negative	210 (16.2)
Missing/unknown subtype	63 (4.9)
Genetic testing	
BRCA1 positive	90 (6.9%)
BRCA2 positive	54 (4.2%)
No mutation detected/VUS****	973 (75.0%)
No testing/Unknown	180 (13.9%)

*In total, 56 (4.3%) women self-identified as Hispanic or Latina.

**Mother or sister.

***Missing/unknown subtype includes cases of DCIS for which HER2 was not performed.

****VUS = variant of unknown significance, VUS = 4.2% (54/1297).

women enrolled were ultimately deemed ineligible). Table 1 summarises the patient characteristics. The mean age at diagnosis was 37 years (range 17–40 years). The majority of the population is white (1101/1297; 84.9%), with a small proportion of Asian, American Indian, Alaskan Native, Black, Haitian, African American and others. Fifty-six women (4.3%) self-identified as Hispanic or Latina. Among participants where family history was available ($n = 1114$), a family history (first-degree relative) of breast or ovarian cancer was self-reported by 176 (15.8%) of the patients. Germline mutation testing was available for 86.1% (1117/1297) of the patients. One thousand two hundred and seventy-six women (98.4%) presented with unilateral breast cancer. The majority of women presented with early-stage invasive disease (7.6% (98/1297) Stage 0; 31.8% (413/1297) Stage I; 40.5% (525/1297) Stage II, 15.2% (197/1297) Stage III; 4.9% [64/1297] Stage IV) and more than half presented with high-grade tumours (752/1297, 58.0%). Most women had hormone receptor-positive disease. Nine hundred and forty-five (72.9%) of the tumours were ER +, and more than one-fourth, 360 (27.8%), were HER2 +.

The distribution of pathologic features by age group is shown in Table 2. Among invasive tumours with the evaluable surrogate molecular phenotype ($n = 1143$; Fig. 1), including multiple tumours in the same patient (11 patients with bilateral tumours), the distribution of subtypes was 32.9% (376/1143) luminal A-like, 42.4% (485/1143) luminal B-like, 8.3% (95/1143) HER2-enriched and 16.4% (187/1143) triple-negative. There were no differences in the distribution of surrogate molecular phenotype by age category. Histologic grade 3 was the most common grade in each age category ($\leq 30 = 58.6%$ (85/146), 31–35 = 59.8% (189/318), and 36–40 years = 55.8% (380/683)). Among the different age groups, there were no significant differences in specific histopathological features evaluated, including the presence of tumour necrosis, lymphocytic infiltration and central fibrotic focus. The highest proportion numerically of Stage IV tumours was observed in the youngest age group (7.5%, ≤ 30 years vs. 5.0%, 31–35 years vs 4.4%, in 36–40 years), though stage distribution was not statistically significantly different between age groups ($P = 0.11$). BRCA mutation status varied significantly by age groups ($P = 0.008$): the frequency of BRCA1 mutations was 6.0% in the 36–40 years group, 8.8% in the 31–35 years and 10.3% in those ≤ 30 years, and the frequency of BRCA2 mutations was 4.7% in 36–40 years, 2.8% in 31–35 years and 4.1% in ≤ 30 years. The majority of invasive tumours were of ductal histologic subtype.

The distribution of surrogate molecular subtype by BRCA mutation status is summarised in Fig. 2. BRCA testing and results were ascertained via medical record review (87.1%, 986/1132) or from survey self-report (9.0%, 102/1132); only 3.9% (44/1132) of women were not tested or had an unknown testing status. Among women who tested positive for a deleterious mutation, 84/131 (64.1%) tumours were in BRCA1 mutation carriers and 47/131 (35.9%) tumours were in BRCA2 mutation carriers. BRCA1 mutation carriers' tumours were more often triple-negative (63.1%, 53/84), followed by 29.8% (25/84) luminal B-like, 4.8% (4/84) HER2-enriched, and 2.4% (2/84) luminal A-like. BRCA2 mutation carriers' tumours were most commonly luminal B-like (55.3%, 26/47), followed by 29.8% (14/47) luminal A-like, 12.8% (6/47) triple-negative, and 2.1% (1/47) HER2-enriched. Interestingly, BRCA2 mutation carriers' tumours were significantly more likely to be luminal B-like/HER2– vs luminal B/HER2 + (38.3% (18/47) vs 17.0% (8/47), $P < 0.0001$). Among the 968 women with a negative test for BRCA1 and BRCA2 mutation or a non-actionable VUS, the most frequent surrogate molecular subtype identified was luminal B-like (42.5%, 412), followed by luminal A-like (35.4% 343), triple-negative (12.9%, 125) and HER2-enriched (9.1%, $n = 88$). Among the 44 women not tested, the most frequent surrogate molecular subtype identified was luminal B-like (50.0%, $n = 22$), followed by luminal A-like (38.6%, 17), triple-negative (6.8%, 3) and HER2-enriched (4.6%, $n = 2$).

Table 2. Distribution of pathologic features by age group.

	Total N = 1147, N (%)	≤30 years, N = 146, N (%)	31–35 years, N = 318, N (%)	36–40 years, N = 683, N (%)	P
Subtype					0.48
Luminal A-like	376 (32.9)	48 (33.1)	98 (30.9)	230 (33.8)	
Luminal B-like	485 (42.4)	61 (42.1)	140 (44.2)	284 (41.7)	
ER and/or PR +, HER2–, grade 3	250 (21.9)	29 (20.0)	70 (22.1)	151 (22.2)	
ER and/or PR +, HER2 +	235 (20.6)	32 (22.1)	70 (22.1)	133 (19.5)	
HER2-enriched	95 (8.3)	12 (8.3)	35 (11.0)	48 (7.1)	
Triple-negative	187 (16.4)	24 (16.6)	44 (13.9)	119 (17.5)	
Missing	4				
Stage					0.11
I	402 (35.1)	44 (30.1)	104 (32.7)	254 (37.2)	
II	502 (43.8)	70 (48.0)	133 (41.8)	299 (43.8)	
III	186 (16.2)	21 (14.4)	65 (20.4)	100 (14.6)	
IV	57 (5.0)	11 (7.5)	16 (5.0)	30 (4.4)	
Histologic subtype					0.11
Ductal	798 (69.6%)	107 (73.3%)	239 (75.2%)	452 (66.2%)	
Lobular	48 (4.2%)	5 (3.4%)	9 (2.8%)	34 (5.0%)	
Ductal and lobular features	114 (9.9%)	13 (8.9%)	26 (8.2%)	75 (11.0%)	
Other	141 (12.3%)	17 (11.6%)	37 (11.6%)	87 (12.7%)	
Unknown	46 (4.0%)	4 (2.7%)	7 (2.2%)	35 (5.1%)	
ER					0.93
Positive	836 (72.9)	108 (74.0)	230 (72.3)	498 (72.9)	
Negative	311 (27.1)	38 (26.0)	88 (27.7)	185 (27.1)	
PR					0.36
Positive	759 (66.2)	92 (63.0)	204 (64.2)	463 (67.8)	
Negative	388 (33.8)	54 (37.0)	114 (35.9)	220 (32.2)	
HER2					0.28
Positive	330 (28.8)	44 (30.1)	105 (33.0)	181 (26.5)	
Negative	814 (71.0)	102 (69.9)	212 (66.7)	500 (73.2)	
Missing	3				
Grade					0.46
I/II	488 (42.7)	60 (41.4)	127 (40.2)	301 (44.2)	
III	654 (57.3)	85 (58.6)	189 (59.8)	380 (55.8)	
Missing	5				
Tumour necrosis					0.73
Yes	178 (15.9)	23 (16.1)	53 (16.8)	102 (15.5)	
No	879 (78.6)	115 (80.4)	247 (78.4)	517 (78.3)	
No answer/NA/missing	90				
Lymphocytic infiltration					0.93
None/Mild	781 (69.9)	105 (73.4)	221 (70.2)	455 (68.9)	
Moderate or marked	309 (27.6)	37 (25.9)	85 (27.0)	187 (28.3)	
No answer/NA/missing	57				
Fibrotic focus					0.27
Yes	136 (12.2)	15 (10.5)	41 (13.0)	80 (12.1)	
No	690 (61.7)	86 (60.1)	184 (58.4)	420 (63.6)	
No answer/NA/missing	321				
Margins					0.05
Pushing/circumscribed	245 (21.9)	40 (28.0)	75 (23.8)	130 (19.7)	
Invasive	642 (57.4)	73 (51.1)	166 (52.7)	403 (61.1)	
No answer/NA/missing	260				
Genetic testing					0.008

Table 2 continued

	Total N = 1147, N (%)	≤30 years, N = 146, N (%)	31–35 years, N = 318, N (%)	36–40 years, N = 683, N (%)	P
<i>BRCA1</i> positive	84 (7.3%)	15 (10.3%)	28 (8.8%)	41 (6.0%)	
<i>BRCA2</i> positive	47 (4.1%)	6 (4.1%)	9 (2.8%)	32 (4.7%)	
<i>BRCA1/2</i> not detected/VUS	972 (84.7%)	123 (84.3%)	276 (86.8%)	573 (83.9%)	
Not tested	44 (3.9%)	2 (1.4%)	5 (1.6%)	37 (5.4%)	

The distribution of surrogate molecular subtype by age stratified by *BRCA1* and *BRCA2* mutation status is shown in Supplementary Tables 1 and 2. Though not statistically significant, the largest proportion of triple-negative cancers among *BRCA1* mutation carriers was seen in women ≤ 30 years (≤ 30 years; 73.3% vs. 60.7% and 61.0%, in 31–35 years and 36–40 years, respectively). In contrast, all the triple-negative cancers among the *BRCA2* mutation carriers were seen in women 36–40 years. Among *BRCA* mutation carriers, the majority of the tumours were of ductal histologic subtype (106/131; 80.9%). Invasive lobular carcinomas were identified in *BRCA2* mutation carriers (3/47; 6.4% of *BRCA2* mutation carriers) but not in *BRCA1* mutation carriers (Supplementary Table 3).

DISCUSSION

Understanding the distinct clinical and pathologic features of breast cancer in young women is critical to mitigating the disparities in outcomes experienced by this population. Instead of comparing young women to an older population of women for whom it is well-recognised, there are differences in stage at presentation, histologic grade and molecular subtype, we sought to evaluate whether there are clinical and pathological differences among young women with breast cancer within our population of patients, expanded fourfold since our prior publication [25]. We continue to see no differences between age groups (≤ 30, 31–35, vs. 36–40 years) and tumour stage, grade or tumour surrogate molecular phenotype among young women with invasive breast cancer.

Among the large proportion of women in our cohort with known *BRCA* status, 86.1% had results available for germline mutations, and 11.1% were *BRCA* mutation carriers (64.1% in *BRCA1* mutation carriers and 35.9% in *BRCA2* mutation carriers). Copson et al. found similar rates of *BRCA* mutation in a large cohort of young women with breast cancer, of which 12.4% were *BRCA* mutation carriers (59.5% in *BRCA1* mutation carriers and 40.5% in *BRCA2* mutation carriers) [22]. In our cohort, the largest proportion of *BRCA* mutation carriers was observed in the youngest group (women ≤ 30 years). Interestingly, others have studied women ≤ 30 years and found a lower proportion of *BRCA* mutation carriers in the very youngest group (women ≤ 25 years) compared to women in the 26–30 year age group [33]. Among the invasive tumours in *BRCA* mutation carriers in our cohort, a few lobular subtypes were identified within the *BRCA2* mutation carriers. Similarly, Mavaddat et al. found significantly more invasive lobular carcinomas among *BRCA2* mutation carriers than among *BRCA1* mutation carriers [34].

We have also demonstrated that tumour surrogate molecular phenotype varies by *BRCA1* and *BRCA2* mutation status among young women (as it does in older women). Larsen et al. studied the molecular phenotype determined by PAM50 within a broad age range (25–74 years) of women and demonstrated that *BRCA1* mutation carriers had proportionally more basal-like tumours (20/33, 61%) and *BRCA2* mutation carriers had proportionally more luminal B subtype (16/22, 73%) [21]. Although this was a small population and the molecular subtype was determined by PAM50, their findings are consistent with those from our cohort in which

BRCA1 mutation carriers' tumours were proportionately more triple-negative (51/82, 62.2%) and *BRCA2* mutation carriers' tumours were most frequently luminal B-like (25/45, 55.6%). Shah et al. identified 50 cases of *BRCA1/2* mutation carriers with ER/PR + and HER2– tumours among all the patients undergoing Oncotype DX testing during an 8-year period, the majority of them were from *BRCA2* mutation carriers (31/50, 62%), supporting the finding of more luminal B-like HER2– tumours among *BRCA2* mutation carriers when compared to *BRCA1* mutation carriers [35]. Similarly, Ha et al. described a higher proportion of triple-negative breast cancers (52/99, 53.3%) among *BRCA1* mutation carriers and luminal B-like cancers (41/103, 39.8%) among *BRCA2* mutation carriers in a broad age range (23–72 years) of women when using immunohistochemistry as a surrogate for molecular phenotype [20]. Although these studies, which both found a high distribution of luminal B-like tumours among *BRCA2* mutation carriers, did not differentiate between luminal B-like HER2 + and luminal B-like HER2– tumours, they did report a high prevalence of HER2– tumours overall among the *BRCA2* mutation carriers, which is consistent with our finding that *BRCA2* mutation carriers are proportionally more likely to develop luminal B/HER2– breast cancer (18/47, 38.3%), irrespective of young age category. Furthermore, Spurdle et al. found that triple-negative phenotype predicted *BRCA1* mutation status, and ER-positive grade 3 phenotype predicted *BRCA2* mutation status, particularly in young women (≤ 50 years) [36].

Mavaddat et al. studied adult women (18 to >70 years) in the Consortium of Investigators of Modifiers of *BRCA 1/2* (CIMBA) and found a decrease in the proportion of triple-negative breast cancers with increasing age among *BRCA1* mutation carriers, and an increase in triple-negative cancers with age at diagnosis among *BRCA2* mutation carriers [34]. In our cohort, the largest proportion of triple-negative cancers among *BRCA1* mutation carriers was similarly seen in the youngest group (women ≤ 30 years). In contrast, all the triple-negative cancers among the *BRCA2* mutation carriers were present in the oldest age group (women 36–40 years). In addition, and in keeping with the findings of Mavaddat et al., there were more ER-positive tumours in the *BRCA2* mutation carriers group than in the *BRCA1* mutation carriers in our cohort [34].

The higher risk of developing breast cancer among women with *BRCA1* or *BRCA2* mutations is well-established, with a lifetime risk described as high as >80% [13]. This has been refined in a recent large prospective cohort of *BRCA1* and *BRCA2* mutation carriers with reported cumulative breast cancer risks to age 80 years of 72% for *BRCA1* mutation carriers and 69% for *BRCA2* mutation carriers [37]. The differences in molecular phenotypes among *BRCA* mutation carriers might have prognostic and predictive implications. For example, in a population-based cohort, Jonasson et al. identified ER-positive status as an adverse prognostic factor in *BRCA2* mutation carriers [38]. Understanding the variations in tumour molecular phenotype by *BRCA1* or *BRCA2* status becomes increasingly important as new breast cancer prevention strategies are developed for asymptomatic *BRCA* mutation carriers not pursuing bilateral prophylactic mastectomies. Strategies that decrease the risk of hormone receptor-negative tumours, such as the use of receptor activator of nuclear factor kappa-B ligand

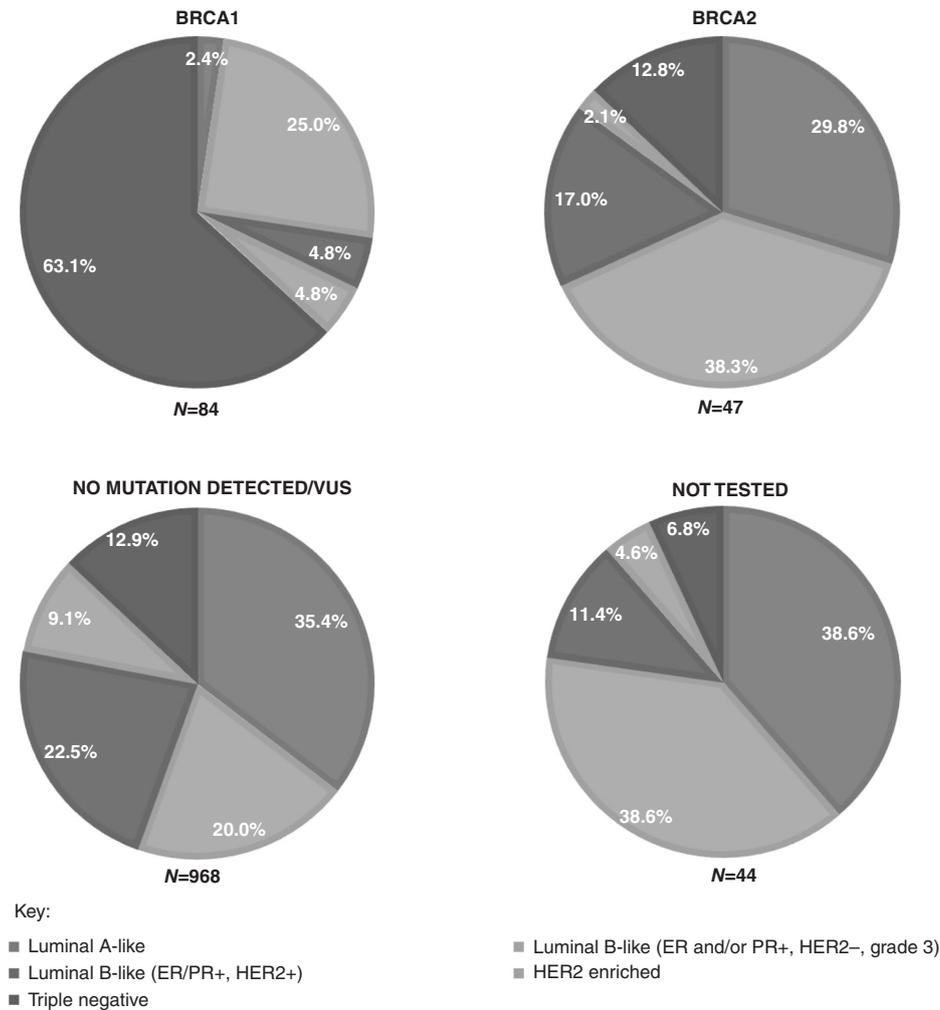


Fig. 2 Distribution of molecular phenotypes among *BRCA1* +, *BRCA2* +, no mutation detected/VUS, and not tested. Each pie chart illustrates the distribution of molecular phenotypes within *BRCA1* ($n = 84$), *BRCA2* ($n = 47$), no mutation detected/VUS ($n = 968$) and patients not tested ($n = 44$).

(RANKL) inhibitors, could be targeted more specifically towards *BRCA1* mutation carriers given that tumours occurring in these women are more likely to be triple-negative [39, 40]. In contrast, tumours that develop among *BRCA2* mutation carriers are more likely to be high grade, ER + luminal B-like, requiring prevention strategies that decrease the risk of hormone receptor-positive tumours. Further research to confirm the intrinsic, unfavourable biology of ER + *BRCA2* breast cancer is clearly warranted. But these differences in molecular phenotypes may explain the relatively recent data from Kotsopoulos et al. which suggest that bilateral oophorectomy prevents early-onset breast cancer among *BRCA2* mutation carriers but not among *BRCA1* mutation carriers [41]. Although the data is controversial, as a protective effect from bilateral oophorectomy in both *BRCA1* and *BRCA2* mutation carriers has been observed in some studies [34, 42–44], and more recently no association between risk-reducing salpingo-oophorectomy and breast cancer risk for either *BRCA1* or *BRCA2* mutation carriers was reported [45]. Furthermore, the distribution of the molecular phenotypes along with the high-risk histopathological features aid in understanding the differences in response to alternative drug targeting for this population, as demonstrated by the beneficial effects of poly ADP ribose polymerase (PARP) inhibitors among *BRCA1* and *BRCA2* mutation carriers with breast cancer [46].

We have confirmed that young women with breast cancer have a greater likelihood of presenting with high-grade tumours, and

have a larger proportion of luminal B-like cancers compared to the general population. Other groups have similarly shown that breast cancers arising in young women are more likely to be of luminal B-like subtype [47–49]. In contrast, some have shown a higher proportion of triple-negative breast cancer among young women [4, 50, 51]. It is important to note that the distribution of the molecular phenotypes differs among different ethnicities, with higher rates of triple-negative and basal-like breast cancer reported among African-American women, interestingly, with a more frequent association with *BRCA2* mutations recently reported in this population [8, 52, 53]. Overrepresentation of white women in our cohort may be a potential reason for the differences in the distribution of the molecular subtypes we observed compared with other publications [4, 50, 51].

Central laboratory testing for the hormonal receptors and HER2 status was not performed in this study. Instead, we abstracted this information from pathology reports. Previous work has compared the results obtained by repeating the ER analysis in a central laboratory and the ER results abstracted from pathology reports and shown high concordance [54]. In addition, we used immunohistochemical results instead of molecular testing to classify tumour phenotype as this has been demonstrated to be an adequate surrogate [31].

One additional potential limitation of this study is the lack of uniformity of how *BRCA* testing was performed. *BRCA* status was

abstracted from the medical record or patient survey and patients were tested in multiple institutions, however, it is important to note that testing during this timeframe would have been performed in a largely consistent manner, through Myriad Genetics. Although the majority of the women had known molecular testing, there are potential variations in the rates of testing during the enrollment period (2006–2016) given the changes in the indications for testing during that timeframe. Other cancer-predisposing gene mutations have been associated with a risk of different subtypes of breast cancer [55]. Given the timing of this cohort, which was mostly accrued pre-panel testing, we do not have available data on the prevalence of other cancer-predisposing gene mutations at this time (e.g., *PALB2*, *TP53*, *CHEK2*, *CDH1*) and future research is needed in this regard, particularly in young breast cancer patients. Lastly, there may also be an element of referral bias, as the majority of participants were identified at large academic medical centres even with our intentional inclusion of community sites.

CONCLUSION

Our consideration of *BRCA1* and *BRCA2* mutation status in a large cohort of young women with breast cancer enhances understanding of the distribution of tumour surrogate molecular subtypes in young women both with and without mutations. The opportunity to provide comparisons across young age groups, and the identification of more aggressive hormone receptor-positive phenotypes in this population also provide direction for future work to further understand and improve the disparate outcomes for young women with luminal B cancers, particularly those with *BRCA2*-associated breast cancer, with potential implications for tailored prevention and treatment.

DATA AVAILABILITY

Available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

Study design and methodology: SMR, AHP and LCC. Data collection: YDGA, HV, CS, JDM and LCC. Data analysis and interpretation: YDGA, SMR, GK, AHP and LCC. Drafting manuscript: YDGA, SMR, AHP and LCC. Critical revisions: SMR, JEG, PDP, KJR, RMT, LS, VFR, SEC, EFB, JDM, EW, AHP and LCC. All the authors approved the final version.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Institutional review board (IRB) approval for the study was obtained through the Dana-Farber/Harvard Cancer Centre and other participating centres. The study was performed in accordance with the Declaration of Helsinki and informed written consent was obtained from all the participants.

CONSENT TO PUBLISH

Not applicable.

COMPETING INTERESTS

Dr. Rulla Tamimi is an editor of the *British Journal of Cancer*. The remaining authors declare no competing interests.

ADDITIONAL INFORMATION

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