Original Article

Prevalence of Germline Variants in Inflammatory Breast Cancer

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BACKGROUND: Inflammatory breast cancer (IBC) is an uncommon and aggressive subtype of breast cancer associated with early disease recurrence and short survival. The prevalence of germline variants in cancer predisposition genes has not been systematically evaluated in women with IBC. **METHODS:** Among 301 women enrolled in the clinical IBC registry at a single institution between 2010 and 2017, 168 had documented genetic testing. A second cohort of 200 IBC cases who had panel-based germline testing performed through a commercial testing laboratory from 2012 to 2017 was added to the analyses. Personal and family cancer histories and genetic testing results were evaluated when they were available for both cohorts. **RESULTS:** Among 501 IBC cases, 368 had documented genetic testing. Germline mutations (56 total) were identified in 53 cases (14.4%). *BRCA1* or *BRCA2* mutations were found in 7.3% of the subjects, 6.3% had a mutation in other breast cancer genes (*PALB2*, *CHEK2*, *ATM*, and *BARD1*), and 1.6% had mutations in genes not associated with breast cancer. The prevalence of mutations was 24% (22 of 92) among women with triple-negative IBC, 13% (13 of 99) among women with estrogen receptor– and/or progesterone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative disease, and 9.3% (10 of 108) among women with HER2-positive IBC. **CONCLUSIONS:** The prevalence and diversity of germline genetic mutations among patients with IBC suggest that further studies should be performed to assess the role of inherited mutations in IBC carcinogenesis in comparison with non-IBC breast cancer. Since IBC has a high metastatic potential associated with poor prognostic outcomes, proposed future studies may also inform targeted treatment options. ***Cancer* 2019;0:1-9**. © *2019 American Cancer Society.*

KEYWORDS: BRCA, DNA repair, germline, inflammatory breast cancer, mutations, pathogenic, variants.

INTRODUCTION

Inflammatory breast cancer (IBC) is an uncommon subtype of breast cancer: it accounts for 1% to 5% of breast cancers diagnosed in the United States.[1,2] Epidemiologic studies have focused on environmental and behavioral risk factors associated with IBC, such as a high body mass index, an earlier age of first pregnancy, and a lower socioeconomic status.[3-5] Geographically, this disease is more prevalent in Middle Eastern countries as well as North Africa.[6-8] In the United States, there continues to be an increased incidence of IBC in African Americans and Arab Americans, regardless of the duration of stay within the continental United States.[9] These data suggest a combination of inherited and environmental risk factors contributing to the development of IBC; however, specific germline genetic susceptibilities for this disease have not yet been elucidated.

One barrier to characterizing an inherited cancer predisposition to IBC stems from the rarity of the disease. In general, genetic testing has been recommended only for women with IBC who also have a family history of breast or ovarian cancer; this is consistent with current National Comprehensive Cancer Network (NCCN) guidelines[10,11] In a single-institution study, the rate of *BRCA1* and *BRCA2* mutations in 105 women with IBC was compared with the rate in a cohort of 1684 women with noninflammatory breast cancer who had been referred for germline genetic testing because of a history suggestive of hereditary breast and ovarian cancer (HBOC).[12] The investigators found that 18.1% of the patients with IBC identified through their genetics program carried a mutation in either *BRCA1* or *BRCA2*; this is higher than the average *BRCA1/2* mutation rate in a general breast cancer cohort with strong family histories indicative of HBOC.[12] However, validation in other IBC cohorts is needed.

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We sought to define the prevalence of germline mutations in known hereditary cancer susceptibility genes in a larger cohort of patients with IBC. Our hypothesis was that IBC may be an independent characteristic associated with a germline cancer predisposition syndrome.

MATERIALS AND METHODS

Patient Cohorts

Clinical IBC cohort

All subjects had been evaluated at the Dana-Farber Cancer Institute and were enrolled in the Inflammatory Breast Cancer Program Registry (a Dana-Farber/Harvard Cancer Center institutional review board–approved registry) from January 1, 2010, through January 1, 2017. After approval had been obtained from the Dana-Farber/Harvard Cancer Center institutional review board, the current study was conducted through a retrospective chart review of 301 individuals with a confirmed diagnosis of IBC as defined by standard diagnostic and clinical criteria of the American Joint Committee on Cancer and a consensus statement on IBC.[13,14] Clinical characteristics were collected and included the age at diagnosis, year of diagnosis, family history of cancer, hormone receptor subtype, genes tested, and germline genetic testing results. The family history was obtained from an abstraction of medical records; the majority (105 of 168 [62%]) had a 3-generation cancer family history pedigree generated by a genetic counselor during a consultation.

Laboratory IBC cohort

A search of the internal databases of cases for which multigene panel testing was performed at Ambry Genetics from an overlapping time period (March 2012 through April 2017) identified 200 subjects with the diagnosis of IBC as reported on clinical test requisition forms. Cases received by Ambry Genetics from the Dana-Farber Cancer Institute were excluded (n = 13). Ambry Genetics assembled de-identified data, including the sex, race/ethnicity, relevant personal and family cancer history, description of the multigene panel ordered, gene sequencing results, and variant classification. The study was determined to be exempt from institutional review board review by the Western institutional review board.

Statistical Analysis

The clinical features and IBC subtype were summarized as numbers and percentages of patients or as medians and interquartile ranges. Features were compared in the clinical cohort between those tested and those not tested with chi-square tests. Among those tested, the prevalence of any mutation was summarized with the 95% confidence interval.

RESULTS

Demographics

The individual IBC cohorts (laboratory and clinical) had nearly identical demographic characteristics except for the IBC subtype, which was more often unknown in the laboratory cohort (Table 1); therefore, the cohorts were combined for this analysis. All 501 subjects were female, and they were predominantly white (70.1%), black (7.2%), and Asian (4.4%). The median age at the diagnosis of IBC was 50 years (interquartile range, 43-59 years). IBC was the first cancer diagnosis in 85.8% of the subjects (430 of 501). Non-IBC breast cancer occurred in 59 of the 501 women (11.8%) before or synchronously with their IBC diagnosis (Table 1). Among the 59 subjects with detailed information available, 29 (49.2%) could be classified as having secondary IBC arising in the ipsilateral breast previously treated for cancer (Supporting Table 1).[15]

The IBC subtype was human epidermal growth factor receptor 2 (HER2-positive) in 33.5% (n = 168), estrogen receptor (ER)–positive and/or progesterone receptor (PR)–positive and HER2-negative in 28.5% (n = 143), and triple-negative (TN; ER-, PR-, and HER2-negative) in 23.8% (n = 119). The IBC subtype was unknown in 14.2% of the subjects (n = 71).

Genetic Testing in the Clinical IBC Cohort

Among the 301 subjects in the IBC clinical cohort, 168 had documented genetic testing (Fig. 1). Those tested were younger at diagnosis than those not tested by an average of 8.6 years (Table 1). The distribution of IBC subtypes and other characteristics did not differ between the tested and untested clinical subjects. Ascertainment of a family history differed by whether subjects had testing or not because the tested group had undergone genetic counseling. Almost half of the subjects (81 of 168 [48.2%]) had multigene panel testing, and 87 had *BRCA* testing only (Supporting Table 2).

Genetic Testing in the Laboratory IBC Cohort

All 200 laboratory subjects underwent multigene panel testing and had 5 to 67 genes analyzed per test. Among these subjects, 32 had limited genetic testing before their panel testing: 29 had previous *BRCA* testing, 1 had *BRCA* and Lynch syndrome testing, 1 had prior *CDKN2A* testing, and 1 had prior *NF1* testing.

TABLE 1. Demographics of Subjects With IBC

	All IBC (n = 501)	Clinical IBC, Not Tested (n = 133)	Clinical IBC, Tested (n = 168)	Laboratory IBC Tested (n = 200)	All Tested IBC (n = 368)
Age at IBC diagnosis, median (IQR), y	50 (43-58.5)	57.2 (50.0-64.4)	48.6 (39.6-55.7)	47 (40.3-53.8)	48 (40.0-55.0)
Race, No. (%)					
White	372 (74.3)	108 (81.2)	133 (79.2)	131 (65.5)	264 (71.7)
Ashkenazi Jewish	21 (4.2)	1 (0.8)	9 (5.4)	10 (5.0)	19 (5.2)
Black	36 (7.2)	9 (6.8)	9 (5.4)	18 (9.0)	27 (7.3)
Asian	22 (4.4)	3 (2.3)	10 (6.0)	9 (4.5)	19 (6.3)
Other	34 (6.8)	7 (5.3)	11 (6.6)	16 (8.0)	27 (7.3)
Unknown	37 (7.4)	6 (4.5)	5 (3.0)	26 (13.0)	31 (8.4)
First cancer diagnosis, No. (%)					
IBC	430 (85.8)	114 (85.7)	147 (87.5)	169 (84.5)	316 (85.9)
Non-IBC BC[a]	59 (11.8)	14 (10.5)	18 (10.7)	27 (13.5)	45 (12.2)
Nonbreast cancer[b]	12 (2.4)	5 (3.8)	3 (1.8)	4 (2.0)	7 (1.9)
IBC Subtype, No. (%)					
TN	119 (23.8)	27 (20.3)	48 (28.6)	44 (22.0)	92 (25.0)
ER/PR+, HER2–	143 (28.5)	44 (33.1)	59 (35.1)	40 (20.0)	99 (26.9)
HER2+	168 (33.5)	60 (22.6)	54 (32.1)	54 (27.0)	108 (29.3)
Unknown	71 (14.2)	2 (1.5)	7 (4.2)	62 (31.0)	69 (18.8)
Family history, No. (%)[c]					
BC/OV	300 (59.9)	65 (48.9)	105 (62.5)	130 (65.0)	235 (63.9)
Other	204 (40.7)	44 (33.1)	78 (46.4)	82 (41.0)	160 (43.5)

Abbreviations: BC, breast cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IBC, inflammatory breast cancer; IQR, interquartile range; OV, ovarian/fallopian tube/primary peritoneal cancer; PR, progesterone receptor; TN, triple-negative (estrogen receptor–, progesterone receptor–, and human epidermal growth factor receptor 2–negative).
[a]Two subjects were diagnosed with synchronous IBC and non-IBC breast cancer.
[b]Nonbreast cancer diagnoses included the following: cervical cancer (n = 1), colon cancer (n = 1), endometrial cancer (n = 2), lung cancer (n = 1), lymphoma (n = 1), melanoma (n = 2), ovarian cancer (n = 1), renal cell carcinoma (n = 2), and thyroid cancer (n = 1). Non-melanoma skin cancer was excluded.
[c]Some subjects had a family history of both BC/OV and Other cancers.

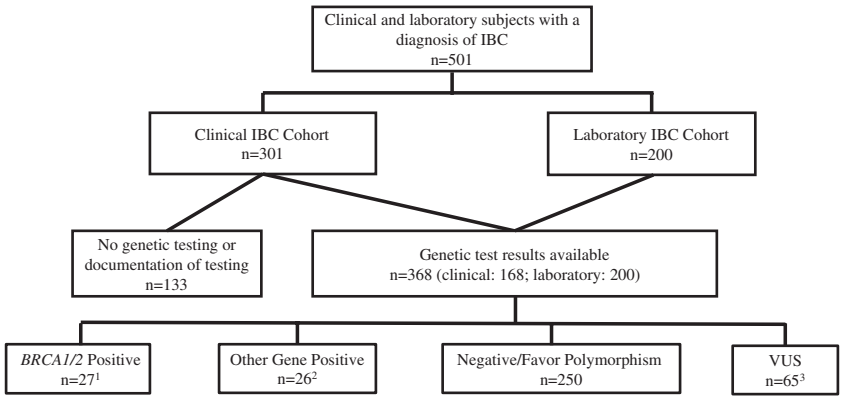

Figure 1. IBC cohorts examined for associations with germline variants. [1]One subject had a mutation in *BRCA2* and *NBN*. [2]Two subjects had 2 mutations: *CHEK2* plus *ATM* and *CHEK2* plus *PTEN*. [3]Seven subjects had mutations and a VUS. Some subjects may have had more than 1 VUS. IBC indicates inflammatory breast cancer; VUS, variant of uncertain significance.

Mutation Prevalence in the Combined Tested IBC Cohorts

Among the 368 subjects in the clinical and laboratory cohorts who had genetic testing completed, pathogenic/likely pathogenic variants were detected in 53 subjects (14.4%; 95% confidence interval, 11.0%-18.4%; Fig. 2A). Three subjects were found to carry 2 germline mutations each (Table 2). Variant-of-uncertain-significance results were obtained for 65 subjects within the tested cohort; however, 7 of these also had a pathogenic/likely pathogenic variant detected (Fig. 1).

Among women with TN IBC (n = 92), 23 mutations were found in 22 subjects (23.9%; Table 2). In contrast, mutations were found in 13.1% of the subjects with ER- and/or PR-positive and HER2-negative disease (13 of 99) and in 9.3% of the subjects with HER2-positive IBC (10 of 108).

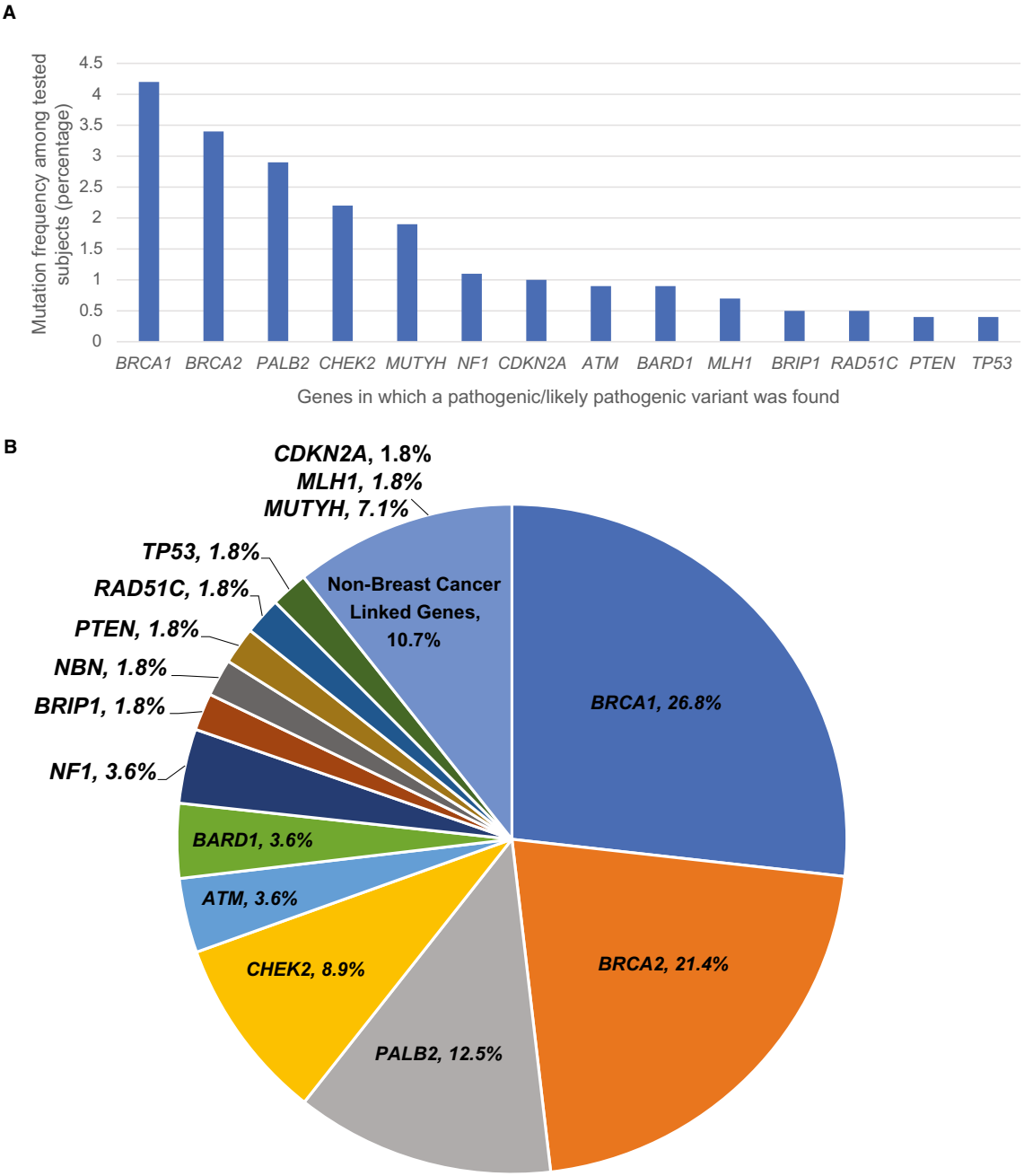

Figure 2. Description of pathogenic/likely pathogenic variants in the tested cohort. (A) Frequency of the pathogenic/likely pathogenic variants among the tested subjects. The total number of tested cases was 368; pathogenic/likely pathogenic mutations were found in 53. This reflects data in Table 3 (pathogenic/likely pathogenic variants identified/total subjects tested per gene). (B) Landscape of the pathogenic/likely pathogenic variants. Fifty-six mutations were identified.

Among the 235 subjects with a family history of breast and/or ovarian cancer, 39 had a pathogenic/likely pathogenic variant (16.6%). Among subjects with a family history of other cancers (prostate, pancreatic, colon, and/or uterine cancer), 20 were found to carry a pathogenic/likely variant (12.5%). These categories were not mutually exclusive.

Among the 368 subjects tested, *BRCA1* or *BRCA2* mutations were found in 7.3% (27/368) of the subjects, 6.3% (23/368) had a mutation in other genes associated with breast cancer, and 1.6% (6/368) had mutations in cancer predisposition genes not clearly associated with breast cancer (Table 3). Three subjects had 2 mutations

TABLE 2. Clinical Characteristics by Genetic Testing Results

Variant Status	Gene (If Applicable)	No. (%)	Age at Diagnosis, Median (IQR), y	Family History, No. (%)		IBC Subtype, No. (%)			
				BC/OV	Other	TN	ER/PR+, HER2–	HER2+	Unknown
All tested		368	48.0 (40.0-55.0)	235	160	92	99	108	69
Negative/VUS		315 (85.6)	48.0 (41.0-56.0)	196 (83.4)	140 (87.5)	70 (76.1)	86 (86.9)	98 (90.7)	61 (88.4)
P/LP		53 (14.4)	44.0 (33.1-53.5)	39 (16.6)	20 (12.5)	22 (23.9)	13 (13.1)	10 (9.3)	8 (11.6)
	ATM	1	46.0	1	1	0	1	0	0
	ATM, *CHEK2*	1	38.0	0	0	0	0	1	0
	BARD1	2	28.0, 30.0	2	2	0	2	0	0
	BRCA1	15	35.1 (30.6-43.6)	12	6	11	2	1	1
	BRCA2	11	52.2 (49.9-59.0)	8	2	6	3	1	1
	BRCA2, *NBN*	1	44.0	1	0	0	0	0	1
	BRIP1	1	51.0	0	0	1	0	0	0
	CDKN2A	1	50.0	1	0	1	0	0	0
	CHEK2	3	36.8	1	0	0	0	0	2
	CHEK2, *PTEN*	1	38.0	1	1	1	0	0	0
	MLH1	1	57.0	0	1	0	0	1	0
	MUTYH-heterozygous	4	45.5 (42.5-52.6)	4	3	0	0	4	0
	NF1	2	52.0, 58.1	1	0	0	1	1	0
	PALB2	7	47 (34.0-60.0)	5	4	2	3	0	2
	RAD51C	1	65.0	1	0	0	0	0	1
	TP53	1	30.0	1	0	0	0	1	0

Abbreviations: BC, breast cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IBC, inflammatory breast cancer; IQR, interquartile range; OV, ovarian cancer; P/LP, pathogenic/likely pathogenic; PR, progesterone receptor; TN, triple-negative (estrogen receptor–, progesterone receptor–, and human epidermal growth factor receptor 2–negative); VUS, variant of uncertain significance.
Cancer diagnoses in first-, second-, and third-degree relatives are included, regardless of the age at diagnosis. A family history of BC or OV includes women with a family history of breast cancer, ovarian cancer, or both. A family history of "other" includes a family history of prostate cancer, pancreatic cancer, colon cancer, and/or uterine cancer. Subjects may have been included in more than 1 category if there was a family history of both BC and prostate cancer, for example.

TABLE 3. Germline Mutations Identified Among 368 Tested Subjects With Inflammatory Breast Cancer

Gene	Women Tested, No. (%)[a]	Mutations, No.	Gene-Specific Mutation Frequency, %
Any P/LP variant	368	56[b]	15.2
Genes related to breast cancer	367 (99.7)	50	13.6
BRCA1 or *BRCA2*	361 (98.1)	27	7.5
BRCA1	361 (98.1)	15	4.2
BRCA2	357 (97.0)	12	3.4
ATM	229 (62.2)	2	0.9
BARD1	215 (58.4)	2	0.9
BRIP1	217 (59.0)	1	0.5
CHEK2	229 (62.2)	5	2.2
NBN	215 (58.4)	1	0.5
NF1	190 (51.6)	2	1.1
PALB2	243 (66.0)	7	2.9
PTEN	276 (75.0)	1	0.4
RAD51C	217 (59.0)	1	0.5
TP53	277 (75.3)	1	0.4
Non–breast cancer genes	224 (60.9)	6	2.7
CDKN2A	101 (27.4)	1	1.0
MLH1	150 (40.8)	1	0.7
MUTYH	216 (58.7)	4	1.9

Abbreviation: P/LP, pathogenic/likely pathogenic.
[a]Reports could not be obtained for 4 subjects who had a panel test. Therefore, the number of patients tested for each gene could be slightly higher.
[b]There were 56 total mutations: 1 patient had pathogenic/likely pathogenic variants in *BRCA2* and *NBN*, 1 patient had pathogenic/likely pathogenic variants in *ATM* and *CHEK2*, and 1 patient had pathogenic/likely pathogenic variants in *PTEN* and *CHEK2*.

identified: *BRCA2* and *NBN*, *CHEK2* and *ATM*, and *PTEN* and *CHEK2*. Of the 56 mutations identified, 48.2% (27 of 56) were in *BRCA1* (15 [26.8%]) and *BRCA2* (12 [21.4%]; Fig. 2B). Other pathogenic/likely pathogenic germline variants identified included *PALB2* (7 [12.5%]), *CHEK2* (5 [8.9%]), *MUTYH* (4 [7.1%]), *ATM* (2 [3.6%]),

TABLE 4. IBC Subtype by Genetic Testing Results and Age at Diagnosis

			Age at Diagnosis, No. (%)		
Subtype	Result	No. (%)	<40 y	40-60 y	>60 y
All IBC	Total	368	91	226	51
	P/LP	49 (13.3)	22 (24.2)	23 (10.2)	4 (7.8)
TN	Total	92	13	68	11
	P/LP	22 (23.9)	8 (61.5)	13 (19.1)	1 (9.1)
ER/PR+, HER2–	Total	99	28	50	21
	P/LP	13 (13.1)	8 (28.6)	4 (8.0)	1 (4.8)
HER2+	Total	108	35	60	13
	P/LP	6 (5.6)	4 (11.4)	2 (3.3)	0 (0.0)
Unknown	Total	69	15	48	6
	P/LP	8 (11.6)	2 (13.3)	4 (8.3)	2 (33.3)

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IBC, inflammatory breast cancer; P/LP, pathogenic/likely pathogenic; PR, progesterone receptor; TN, triple-negative (estrogen receptor–, progesterone receptor–, and human epidermal growth factor receptor 2–negative).
Four subjects with heterozygous *MUTYH* mutations are counted as negative in this table.

BARD1 (2 [3.6%]), and *NF1* (2 [3.6%]). When adjustments were made for the number of subjects tested per gene, the mutation frequencies were as follows: 2.9% for *PALB2*, 2.2% for *CHEK2*, 1.9% for *MUTYH*, 0.9% for *ATM*, 0.9% for *BARD1*, and 1.1% for *NF1* (Table 3 and Supporting Table 3). Of the *CHEK2* mutations, 2 were c.1100delC/p.Thr367Metfs, and no founder, low-penetrance mutations (c.470T>C/p.I157T, c.1283C>T/p.S428F) were identified. Mutations in the following genes were present in 1 subject each (1.8%): *BRIP1*, *NBN*, *CDKN2A*, *PTEN*, *MLH1*, *RAD51C*, and *TP53*.

IBC Subtype by Age and Genetic Test Result

In an effort to evaluate clinical characteristics predictive of germline mutations, we examined the IBC subtype by the age at diagnosis and the genetic test result type (Table 4). For this analysis, *MUTYH*-heterozygous subjects were included in the negative group because this was not known to confer an increased risk for breast cancer. Notably, all 4 *MUTYH*-heterozygous subjects had HER2-positive IBC. The mutation prevalence was highest in subjects diagnosed with IBC at an early age, as would be expected. Of the 13 subjects with TN IBC diagnosed at an age younger than 40 years, 8 (61.5%) were found to carry a pathogenic/likely pathogenic germline variant. Among the subjects diagnosed with ER- and PR-positive/HER2-negative disease and those with HER2-positive disease younger than 40 years, 8 of 28 (28.6%) and 4 of 35 (11.4%), respectively, were found to carry a pathogenic/likely pathogenic variant. Unlike the TN IBC subjects, subjects with non-TN IBC were found to have a higher frequency of pathogenic/likely pathogenic variants when undergoing panel testing rather than *BRCA* testing only (Supporting Table 4). Rates of positive germline results were 2 times higher across all age ranges for women with TN IBC versus women with IBC of other subtypes.

DISCUSSION

We evaluated a total of 501 subjects with IBC identified through the Inflammatory Breast Cancer Registry at the Dana-Farber Cancer Institute and through Ambry Genetics and determined that 14.4% of the 368 individuals who underwent genetic testing carried a pathogenic/likely pathogenic germline variant in cancer predisposition genes. Most of these mutations were detected in actionable, high-penetrance cancer susceptibility genes. The most common mutations were found in the *BRCA1* and *BRCA2* genes (7.3% of tested subjects and 48.2% of identified mutations).

These data not only quantify the frequency of *BRCA1* and *BRCA2* mutations in tested subjects with IBC but also provide perspective on the landscape of non-*BRCA1*/*BRCA2* mutations in this rare disease. In the subset of cases completing more expansive genetic testing, we also identified additional breast cancer predisposition genes, including *PALB2*, *CHEK2*, *BARD1*, and *ATM*. Although mutations in other cancer predisposition genes (*CDKN2A*, *MLH1*, and *MUTYH*) were identified, the implications of these mutations for breast cancer carcinogenesis are unclear.

These analyses also provide insight into the subtype of IBC, age at diagnosis, and family history among subjects with pathogenic/likely pathogenic germline variants. The highest prevalence of germline mutations was found in subjects with TN IBC diagnosed at an age younger than 40 years (61.5%). In patients from the United Kingdom with triple-negative breast cancer (TNBC) diagnosed at an age younger than 50 years, the prevalence of *BRCA1* mutations was 22%.[16] A second study of 199 subjects with TNBC found a *BRCA1* or *BRCA2* mutation frequency of 15.1% among those diagnosed at an age younger than 50 years, regardless of the family cancer history.[17] Lastly, in a recent multigene panel–based testing cohort of 1824 TNBC subjects, 20% of the cases diagnosed at an age younger than 35 years and 23% of those diagnosed at an age younger than 40 years had a mutation in a breast cancer susceptibility gene.[18] Although some of the TNBC cases in the aforementioned cohorts may have been inflammatory,

the 3-fold higher frequency of germline mutations in our selected IBC cohort is compelling.

Our group has previously published the results of multigene panel testing among women with non-IBC breast cancer evaluated at our center.[19] The previously published cohort was subject to the same referral biases as our current study, and this makes it a reasonable comparator. The overall frequency of germline mutations was 10.7%, whereas in our current analysis of IBC, the prevalence of pathogenic/likely pathogenic variants was higher (14.4%). In Tung et al's study,[19] the prevalence of germline mutations varied according to the breast cancer subtype: 17.2% in TN disease, 8.6% in ER- and PR-positive/HER2-negative disease, and 10.8% to 11.1% in HER2-positive disease. More recently, a study of 8753 TNBC subjects found a mutation rate of 14.4% through a 17-gene panel test.[20] In our current analysis, the overall prevalence of germline mutations was also higher in the TN (24%) and ER- and PR-positive/HER2-negative subtypes (13%), but the prevalence was lower in IBC subjects with HER2-positive disease (5.6%).

Our findings are consistent with others demonstrating a high rate of mutations in *BRCA1* and *BRCA2* among subjects with IBC. In a study of 105 IBC subjects who completed only *BRCA1* and *BRCA2* testing, 18.1% (n = 19) were found to carry a pathogenic/likely pathogenic germline variant.[12] Neither our study nor previous studies have been able to quantify the mutation rate among IBC subjects diagnosed at an older age of onset or with HER2-positive disease because these groups seldom meet genetic testing criteria under the current NCCN guidelines.[11] These studies underscore the need for further investigations; specifically, either case-controlled comparisons of multigene panel testing in patients with IBC versus non-IBC or prospective, uniform panel testing of serial, unselected IBC cases is required for unbiased mutation prevalence estimates.

Among the 501 subjects in our cohort, 11.8% (n = 59) developed secondary IBC arising in the setting of a previous diagnosis of a noninflammatory breast cancer. Pathogenic/likely pathogenic variant carriers had a shorter interval to secondary IBC than subjects with negative or variant-of-uncertain-significance results. Although secondary IBC has been described, the frequency remains unknown, and its association with germline mutations has not been elucidated.

NCCN guidelines have provided a framework for identifying patients with breast cancer who may be at high risk for carrying a mutation in a cancer predisposition gene.[11] Subjects with TNBC diagnosed at an age younger than 60 years, regardless of further history, are considered appropriate for HBOC genetic testing. However, there is a mounting body of evidence indicating mutation frequencies of 5% in TNBC cases without the requisite family history or age restrictions.[18] There are no guidelines for the testing of HER2-positive individuals, and this adversely affects the IBC population because of the high prevalence of HER2-positive disease (up to 40%).[21] It is notable that 133 of the 301 subjects in our clinical cohort (44.2%) did not have documented genetic testing. Our untested clinical cohort was older at the age of IBC diagnosis than the tested clinical cohort, but other characteristics, including subtype and family history, did not differ. Currently, patients with IBC are referred for germline testing on the basis of classic HBOC characteristics without a specialized approach for hereditary risk assessment in IBC cases.

As with many cancer genetics studies, generalization of our findings to diverse populations is limited because only 29.9% of the subjects within our cohort were nonwhite. Although this reflects pervasive racial disparities in genetic counseling and testing,[22] the impact in IBC may be particularly pronounced because the disease disproportionately affects black women.[23] Another limitation of our analysis is that subjects older than 60 years and those with HER2-positive IBC were poorly represented in the tested cohort, and this potentially limits the generalizability of these findings, although this is the subject of an ongoing study at our institution. Almost half of the clinical cohort had *BRCA1/2* testing only (23.6% of the total cohort); thus, the frequency of germline mutations in IBC may be underestimated because not all subjects had testing for a comprehensive set of breast cancer genes. Although the reported frequency of IBC as a second breast cancer was interesting, it may reflect an ascertainment bias in terms of who is referred for genetic testing. In the laboratory cohort, the diagnosis of IBC was obtained from a test requisition form or clinic note. Although this may be considered a limitation, we would argue that there is a high degree of specificity in reporting IBC, and it is much more likely that this detailed information is underreported rather than overreported or misreported on test requisition forms or in genetic counseling sessions. Furthermore, a laboratory-based quality analysis of breast cancer reporting on test requisitions in comparison with clinic notes demonstrated a high level of accuracy of reporting for breast cancer cases.[24] Lastly, the majority of family cancer histories from the clinical cohort were obtained by a genetic counselor; however, this process was not uniform in the combined cohort and is a limitation.

Germline genetic testing of patients with cancer has become a critical component of cancer care, in that it can inform options for treatment and affect personal and family screening recommendations for other malignancies, including breast cancer. The prevalence of germline mutations among IBC cases in the current study suggests the need for further investigation to delineate the diversity of inherited mutations and determine their role in the development of IBC versus non-IBC. Because of the poor long-term survival associated with IBC, information about the presence of cancer predisposition genes will become increasingly important as new therapies become available for cancers associated with germline mutations.[25-27]

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AUTHOR CONTRIBUTIONS

Huma Q. Rana: Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, and writing (original draft, review, and editing). **Rosalba Sacca:** Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, and writing (original draft, review, and editing). **Christine Drogan:** Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, and writing (original draft, review, and editing). **Stephanie Gutierrez:** Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, and writing (original draft, review, and editing). **Emily Schlosnagle:** Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, and writing (original draft, review, and editing). **Meredith M. Regan:** Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, and writing (original draft, review, and editing). **Virginia Speare:** Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, and writing (original draft, review, and editing). **Holly LaDuca:** Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, and writing (original draft, review, and editing). **Jill Dolinsky:** Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, and writing (original draft, review, and editing). **Judy E. Garber:** Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, and writing (original draft, review, and editing). **Beth A. Overmoyer:** Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, and writing (original draft, review, and editing).

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