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Relative contributions of *BRCA1* and *BRCA2* mutations to “triple-negative” breast cancer in Ashkenazi Women

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Abstract

Approximately 10% of Ashkenazi Jewish (AJ) women with breast cancer (BC) carry a founder mutation in *BRCA1* or *BRCA2*. There is an association between *BRCA1* mutations and “triple-negative” breast cancer (TNBC) [estrogen receptor (ER) and progesterone receptor (PR) negative, HER2 negative]. We sought to determine the predictive value of the TNBC phenotype for the presence of a *BRCA* mutation in AJ women ascertained without respect to family history. DNA samples were collected between 8/2000 and 6/2004 from a prevalent cohort of unselected AJ women with breast cancer (median age at diagnosis 56 years). Samples ($n = 451$) were genotyped for AJ founder mutations. 352 (78.0%) cancers were ER positive, 254 (56.3%) PR positive, and 91 (20.2%) ER negative/PR negative. 63 (14.0%) cancers were HER2 positive (immunohistochemistry 3+ or FISH>2.2). TNBC was observed in 64 patients (14.2%). Founder mutations were detected in 48 samples (10.6%) including 25/64 TNBC (39.1%; 19 *BRCA1*, 6 *BRCA2*). Among TNBC patients with family history (FH) information, 6/15 (40%) mutations were found in women without breast or ovarian cancer in a close relative. The positive predictive

value of TNBC for a *BRCA1* mutation was 30% overall, 50% in women diagnosed <50 years, and 14% in women diagnosed ≥ 50. TNBC was significantly associated with detecting a mutation in either *BRCA1* or *BRCA2*, but only 25/52 (48%) mutation-associated cancers were TNBC. The prevalence of *BRCA* founder mutations exceeds 50% in subsets of AJ women with TNBC. FH is an imperfect predictor of mutation status in this group. A significant number of mutation-associated TNBC are due to *BRCA2*.

Keywords

BRCA1; *BRCA2*; Ashkenazi; Triple-negative breast cancer

Introduction

BRCA1-associated breast cancers (BCs) often manifest a “basal-like” gene expression profile and a “triple-negative” immunohistochemistry (IHC) profile [estrogen receptor (ER) and progesterone receptor (PR) negative, HER2 non-overexpressing]. Gene expression profiling has provided a greater understanding of the heterogeneity of triple-negative breast cancer (TNBC), revealing an association between *BRCA1* mutation carriers, “basal-like” tumors and the TNBC phenotype [1, 2]. The relationship between these entities has been reviewed extensively elsewhere [3, 4]. The TNBC phenotype may be an useful adjunct to empiric *BRCA* mutation prediction models when developing estimates of mutation probability [5].

The *BRCA* founder mutations *BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 6174delT are found in approximately 2.5% of individuals of Ashkenazi descent (Eastern and Central European Jewish ancestry) [6]. Approximately 10% of all Ashkenazi women with BC carry one of these three mutations [7]. The prevalence of mutations in young Ashkenazi BC patients is even higher. Previous studies of the association between TNBC phenotype and *BRCA* mutations have either limited the analysis to *BRCA1* mutations in women with TNBC or have studied selected women ascertained on the basis of early onset disease or a strong family history. We sought to examine the impact of TNBC immunophenotype in a broader context by determining the likelihood of detecting a *BRCA1* or *BRCA2* founder mutation in an unselected cohort of Ashkenazi women with BC.

Methods

Study population

Between 8/2000 and 6/2004, we ascertained DNA samples from women undergoing treatment for BC at Memorial Sloan-Kettering Cancer Center. This report is limited to the 451 subjects who described Jewish religious preference [highly correlated (>90%) with Eastern or Central European (Ashkenazi) ancestry at this institution] and for which data were available regarding hormone receptor and HER2 status. The collected samples were derived from EDTA-anticoagulated blood remaining after clinical laboratory testing, mainly from inpatients. Ascertainment was not selected for age at diagnosis or family history. Samples were annotated with limited demographic and clinic-pathologic information (specifically hormone receptor and HER2 status). The presence or absence of a family history of BC in a first or second-degree relative was abstracted from the medical record. The subject was considered to have TNBC if fewer than 10% of cells demonstrated nuclear staining for estrogen and PR, and if staining for HER2 was either 0–1+ or 2+ with FISH <2.0. All IHC information was determined by review of existing pathology records and IHC was not repeated.

After sample annotation, each sample was assigned an unique study ID corresponding to the database record describing the clinicopathologic features of that sample. All links between sample IDs and the patient identifiers were then irretrievably destroyed to anonymize the samples, according to procedures used in other retrospective cohort studies. The sample ascertainment protocol and anonymization procedures were approved by the Institutional Review Board.

Genotyping

After DNA extraction according to standard protocols, and anonymization according to the above schema, samples were genotyped for the Ashkenazi *BRCA* founder mutations (*BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 6174delT) as previously described [8].

Statistics

Descriptive statistics for the study population were calculated. Characteristics of mutation carriers and non-mutation carriers were compared using non-parametric tests for continuous variables. The prevalence of mutations in different clinical subsets was compared using χ^2 tests as appropriate. Analyses were conducted using SPSS version 16.0 (SPSS, Inc). 95% confidence intervals for proportions were calculated by the method of Wilson as implemented by Newcombe [9, 10].

Results

The characteristics of the 451 subjects are presented in Table 1. *BRCA* founder mutations were detected in 48 samples (10.6%, 95% CI 8.1–13.8%). There were 27 samples (6.0%) with *BRCA1* mutations and 21 samples (4.7%) with *BRCA2* 6174delT.

The TNBC was diagnosed in 64/451 subjects (14.2%, 95% CI 11.3–17.7%). *BRCA* founder mutations were identified in 25/64 (39.1%, 95% CI 28.1–51.3%) women with TNBC (19 *BRCA1*, 6 *BRCA2*). Mutations in women with TNBC were found more often in *BRCA1* rather than *BRCA2* ($P = 0.001$). Conversely, most women with *BRCA1* mutations had TNBC (19/27). However, a significant proportion of women with *BRCA2* mutations (6/21) also had TN disease.

Founder mutations were more common in women who were younger at diagnosis of TNBC, although there was still appreciable mutation prevalence in women who were over 50 at diagnosis of TNBC (16/28 women under 50 at diagnosis of TNBC vs. 9/36 women over 50, $P = 0.01$) (Table 2). The association of mutation status with age at TNBC diagnosis was mostly ascribable to *BRCA1* mutations. The prevalence of *BRCA1* mutations in young women with TN disease was 14/28 (50.0%, 95% CI 32.6–67.4%) compared to 5/36 (13.9%, 95% CI 6.1–28.7%) in women diagnosed with TNBC after age 50 ($P = 0.002$). The prevalence of *BRCA2* mutations in younger and older women with TNBC was not significantly different (2/28 vs. 4/36; $P = 0.7$). *BRCA1* and *BRCA2* founder mutations were equally prevalent in women diagnosed with TNBC at age 50 or older (5/36 *BRCA1* vs. 4/36 *BRCA2*).

The *BRCA* founder mutations were detected in 5.9% (23/387) of women with non-TNBC, including 4.7% (13/275) of women over age 50 at diagnosis. Mutations were significantly more common in women with TNBC than with non-TNBC (25/64 vs. 23/387; $P < 0.001$). However, the majority of mutations (25/48, 52.1%) were not found in women with TNBC.

Several characteristics were examined for their association with the presence of a *BRCA* founder mutation in this unselected group. Among women whose family history was documented in the medical record, women with mutations were significantly more likely to

have a family history of BC (23/37 vs. 153/356, $P = 0.04$). Family history information was available in the medical record for 43 women with TNBC. Of these, mutations were identified in 6/15 (40.0%) without a documented history of breast and ovarian cancer in a first or second-degree relative and in 9/28 (32.1%) with a documented family history ($P = 0.5$). Women with mutations were significantly younger than those without (mean age 49.6 vs. 58.1 years, $P < 0.001$), but 10 mutations (2 *BRCA1*, 8 *BRCA2*) were found among the 186 women who were 60 or older at diagnosis (5.4%). The difference in age at diagnosis was more obvious for *BRCA1* carriers (45.5 vs. 58.1 years, $P < 0.001$) than for *BRCA2* carriers (54.1 vs. 58.1 years; $P = 0.46$). Founder mutations were more common in women under 50 at diagnosis (26/140 under 50 vs. 22/311 over 50; $P < 0.001$), women with ER negative disease (29/99 vs. 19/352; $P < 0.001$), and women with PR negative disease (32/197 vs. 16/254; $P = 0.001$). In the group as a whole (not limited to women with TNBC), among women whose family history was documented, mutations were more common in women with a family history of breast or ovarian cancer than in those without such a history (23/176 vs. 14/217, $P = 0.03$). *BRCA1* mutations were more common in women under 50 at diagnosis ($P < 0.001$), women with ER negative disease ($P < 0.001$), and women with PR negative disease ($P < 0.001$). *BRCA2* 6174delT was not significantly associated with age at diagnosis, ER status, or PR status.

Discussion

This study evaluated the relationship of phenotype to *BRCA1/2* founder mutation status and the predictive value of TNBC for *BRCA1/2* mutations in a hospital-based ascertainment of Ashkenazi women. We affirm the previously reported striking association of TNBC with *BRCA1* mutations, particularly among women under age 50. More than half of the Ashkenazi women younger than age 50 with TNBC carried a *BRCA* founder mutation. This supports the general recommendation that younger women with TNBC be referred for genetic testing [11]. The association between TNBC and founder mutations was not limited to young women. Although the sample size was small, a significant proportion of older women (>50 years at diagnosis) with TNBC also carried mutations in *BRCA1* (13.9%) or *BRCA2* (11.1%). A meaningful proportion of mutation carriers with TNBC did not have a documented family history of breast or ovarian cancer, although family history information for this group was not gathered through genetic counseling and may have been under documented. However, in another recent study of unselected TNBC in which mutations were sought in tumor tissue, 9/14 germ-line *BRCA1* mutation carriers did not have a first-degree family history of breast or ovarian cancer [12]. This suggests that AJ women with TNBC may be candidates for *BRCA* mutation testing even in the absence of such a history, especially if they are young. Despite the strong association between TNBC and *BRCA* mutations, limiting genetic testing to women with TNBC is not an effective strategy in this population, as most founder mutations in this group (27/52, 51.9%) were not associated with TNBC.

Our study was limited to Ashkenazi women from a specific geographic area, and testing was limited to the three common founder mutations. Two other studies have described mutation prevalence in this ethnic group [13, 14]. Foulkes et al. [13] identified *BRCA1* founder mutations in 17/72 (23.6%) ER negative/HER2 negative samples, slightly less than the nearly 30% prevalence in this study. Karp et al. [14] reported *BRCA1* mutations in 13/46 (28%) Ashkenazi women with ER negative BC (HER2 not described). Neither study found a significant *BRCA2* mutation prevalence in women with ER negative BC. These studies, like this study, were hospital-based ascertainties of Ashkenazi women without regard to family history, but it is possible that differences in age distribution within the studies may explain the differences in mutation prevalence between studies. Young (<50 years) women were over-represented in the present study, comprising 30% of the patients. The presence of

a relatively high number of young women would be expected to skew mutation prevalence upwards. However, we did also identify mutations in a clinically relevant proportion (25%) of women who were older than 50 at the time of their diagnosis of TNBC, including 2 women with *BRCA2* mutations (8% of all mutation carriers) who were diagnosed with TNBC after age 65, the ascertainment age cut-off in other reports.

Unlike other studies, we found that a significant proportion of *BRCA2*-associated BCs in AJ women were TNBC. Nearly 10% of the TNBC in this series were associated with *BRCA2* 6174delT. Adding these women to the *BRCA1* mutation carriers brought the overall founder mutation prevalence in TNBC in our study to nearly 40%. Conversely, 24% of *BRCA2*-associated cancers in this series were TNBC, which contrasts with the marked ER positive predominance of *BRCA2* mutation-associated BC in other studies. It is possible that some of the *BRCA2*-associated cancers expressed ER at a low level (between 2 and 10% of cells) and thus might not have been classified as TNBC by more recent guidelines [15]. In this dataset, ER negativity was determined on the basis of clinical reporting, which employed a threshold of 10% of cells at the time these samples were ascertained. Because of the anonymization schema required to perform this study, it was not possible to reconfirm the level of ER expression in these cases. In addition, most of the subjects of this study were ascertained as inpatients, and many were presumably suffering from metastatic disease. It is possible that the negative prognosis of TNBC may also have led to over-representation of *BRCA2* carriers in TNBC in this dataset. However, Atcheley et al. [16] also identified *BRCA2* mutations in 7.5% of the women with TNBC evaluated in their clinic-based ascertainment (18% of all mutations in TNBC in their series). This suggests that our observation of *BRCA2* mutations in TNBC is not likely to be exclusively the result of misclassification.

The prevalence of mutations among Ashkenazi women with TNBC is likely to be higher than that in more diverse populations without founder mutations. However, the observation that older women with TNBC may have *BRCA* mutations may hold true in out-bred populations [17]. Founder mutation testing may have failed to identify some mutations; however, the number of mutations that would be found by more extensive sequencing is likely to be low [18, 19]. Finding more mutations would further increase the estimated mutation prevalence in TNBC. Mutations identified by sequencing would more likely be *BRCA2* associated mutations as most Ashkenazi non-founder mutations are associated with *BRCA2* [20]. Thus, more complete sequencing would be unlikely to change the observation that constraining testing to *BRCA1* in TNBC would be an unwise strategy.

A number of other groups have evaluated the prevalence of *BRCA* mutations in women with TNBC (summarized in Table 3). Despite the fact that many of these investigations were not restricted to Ashkenazi women, these studies were generally consistent in identifying mutations in approximately 25% of patients with TNBC. Some of these studies only examined the association between TNBC and *BRCA1* mutations, and thus may have underestimated the total mutation prevalence (when including both *BRCA1* and *BRCA2*) [13, 21]. In support of this hypothesis, Atchley et al. [16] included *BRCA2* mutation analysis and reported the overall prevalence of mutations to be approximately 40%, nearly exactly the same as the 39% prevalence in our study.

In conclusion, this study provides detailed information regarding the relationships between age at diagnosis, triple-negative immunophenotype, and mutation prevalence in Ashkenazi women with BC. We found a striking prevalence of *BRCA* mutations among young (<50) AJ women with TNBC, and an appreciable prevalence among older TNBC patients and those with no documented family history of breast or ovarian cancer. We found that the association between TNBC and *BRCA* mutations was not limited to *BRCA1*, and that a

significant proportion of women with TNBC had *BRCA2* mutations. The results of our study suggest that AJ women with TNBC should be offered complete founder mutation testing, including *BRCA2* 6174delT, irrespective of age at diagnosis or family history.

References

1. Perou CM, Jeffrey SS, van de Rijn M, Rees CA, Eisen MB, Ross DT, Pergamenschikov A, Williams CF, Zhu SX, Lee JC, Lashkari D, Shalon D, Brown PO, Botstein D. Distinctive gene expression patterns in human mammary epithelial cells and breast cancers. *Proc Natl Acad Sci USA*. 1999; 96(16):9212–9217. [PubMed: 10430922]
2. Rakha EA, Reis-Filho JS, Ellis IO. Basal-like breast cancer: a critical review. *J Clin Oncol*. 2008; 26(15):2568–2581.10.1200/JCO.2007.13.1748 [PubMed: 18487574]
3. Turner NC, Reis-Filho JS. Basal-like breast cancer and the *BRCA1* phenotype. *Oncogene*. 2006; 25(43):5846–5853.10.1038/sj.onc.1209876 [PubMed: 16998499]
4. Turner N, Tutt A, Ashworth A. Hallmarks of ‘*BRCAness*’ in sporadic cancers. *Nat Rev Cancer*. 2004; 4(10):814–819.10.1038/nrc1457 [PubMed: 15510162]
5. Evans DG, Lalloo F, Cramer A, Jones EA, Knox F, Amir E, Howell A. Addition of pathology and biomarker information significantly improves the performance of the Manchester scoring system for *BRCA1* and *BRCA2* testing. *J Med Genet*. 2009; 46(12):811–817.10.1136/jmg.2009.067850 [PubMed: 19542080]
6. Struwing JP, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, Timmerman MM, Brody LC, Tucker MA. The risk of cancer associated with specific mutations of *BRCA1* and *BRCA2* among Ashkenazi Jews. *N Engl J Med*. 1997; 336(20):1401–1408.10.1056/NEJM199705153362001 [PubMed: 9145676]
7. Robson ME, Chappuis PO, Satagopan J, Wong N, Boyd J, Goffin JR, Hudis C, Roberge D, Norton L, Begin LR, Offit K, Foulkes WD. A combined analysis of outcome following breast cancer: differences in survival based on *BRCA1/BRCA2* mutation status and administration of adjuvant treatment. *Breast Cancer Res*. 2004; 6(1):R8–R17.10.1186/bcr658 [PubMed: 14680495]
8. Zhang L, Kirchhoff T, Yee CJ, Offit K. A rapid and reliable test for *BRCA1* and *BRCA2* founder mutation analysis in paraffin tissue using pyrosequencing. *J Mol Diagn*. 2009; 11(3):176–181.10.2353/jmoldx.2009.080137 [PubMed: 19324993]
9. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. *Stat Med*. 1998; 17(8):857–872. [PubMed: 9595616]
10. Wilson EB. Probable inference, the law of succession, and statistical inference. *J Am Stat Assoc*. 1927; 22(158):209–212.
11. Kwon JS, Gutierrez-Barrera AM, Young D, Sun CC, Daniels MS, Lu KH, Arun B. Expanding the criteria for *BRCA* mutation testing in breast cancer survivors. *J Clin Oncol*. 2010; 28(27):4214–4220.10.1200/JCO.2010.28.0719 [PubMed: 20733129]
12. Gonzalez-Angulo AM, Timms KM, Liu S, Chen H, Litton J, Potter J, Lanchbury JS, Stemke-Hale KA, Hennessy B, Arun BK, Hortobagyi GN, Do K-A, Mills GB, Meric-Bernstam F. Incidence and outcome of *BRCA* mutations in unselected patients with triple receptor-negative breast cancer. *Clinical Cancer Research*. 2011; 10.1158/1078-0432.ccr-10-2560
13. Foulkes WD, Stefansson IM, Chappuis PO, Begin LR, Goffin JR, Wong N, Trudel M, Akslen LA. Germline *BRCA1* mutations and a basal epithelial phenotype in breast cancer. *J Natl Cancer Inst*. 2003; 95(19):1482–1485. [PubMed: 14519755]
14. Karp SE, Tonin PN, Bégin LR, Martinez JJ, Zhang JC, Pollak MN, Foulkes WD. Influence of *BRCA1* mutations on nuclear grade and estrogen receptor status of breast carcinoma in Ashkenazi Jewish women. *Cancer*. 1997; 80(3):435–441. [PubMed: 9241077]
15. Hammond ME, Hayes DF, Wolff AC, Mangu PB, Temin S. American society of clinical oncology/college of american pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Oncol Pract*. 2010; 6(4):195–197.10.1200/JOP.777003 [PubMed: 21037871]
16. Atchley DP, Albarracin CT, Lopez A, Valero V, Amos CI, Gonzalez-Angulo AM, Hortobagyi GN, Arun BK. Clinical and pathologic characteristics of patients with *BRCA*-positive and *BRCA*-

- negative breast cancer. *J Clin Oncol*. 2008; 26(26):4282–4288.10.1200/JCO.2008.16.6231 [PubMed: 18779615]
17. Kandel, MJ.; Stadler, Z.; Masciari, S., et al. Prevalence of *BRCA1* mutations in triple negative breast cancer (BC). *J Clin Oncol*; ASCO Annual Meeting Proceedings Part I; 2006 Jun 20. Supplement
 18. Distelman-Menachem T, Shapira T, Laitman Y, Kaufman B, Barak F, Tavtigian S, Friedman E. Analysis of *BRCA1/BRCA2* genes' contribution to breast cancer susceptibility in high risk Jewish Ashkenazi women. *Fam Cancer*. 2009; 8(2):127–133.10.1007/s10689-008-9216-6 [PubMed: 18798010]
 19. Laitman Y, Borstein RT, Stoppa-Lyonnet D, Dagan E, Castera L, Goislard M, Gershoni-Baruch R, Goldberg H, Kaufman B, Ben-Baruch N, Zidan J, Maray T, Soussan-Gutman L, Friedman E. Germline mutations in *BRCA1* and *BRCA2* genes in ethnically diverse high risk families in Israel. *Breast Cancer Res Treat*. 201010.1007/s10549-010-1217-0
 20. Kauff ND, Perez-Segura P, Robson ME, Scheuer L, Siegel B, Schluger A, Rapaport B, Frank TS, Nafa K, Ellis NA, Parmigiani G, Offit K. Incidence of non-founder *BRCA1* and *BRCA2* mutations in high risk Ashkenazi breast and ovarian cancer families. *J Med Genet*. 2002; 39(8): 611–614. [PubMed: 12161607]
 21. Chang J, Hilsenbeck SG, Sng JH, Wong J, Ragu GC. Pathological features and *BRCA1* mutation screening in premenopausal breast cancer patients. *Clin Cancer Res*. 2001; 7(6):1739–1742. [PubMed: 11410514]
 22. Lidereau R, Eisinger F, Champeme MH, Nogues C, Bieche I, Birnbaum D, Pallud C, Jacquemier J, Sobol H. Major improvement in the efficacy of *BRCA1* mutation screening using morphoclinical features of breast cancer. *Cancer Res*. 2000; 60(5):1206–1210. [PubMed: 10728676]
 23. Haffty BG, Choi DH, Goyal S, Silber A, Ranieri K, Matloff E, Lee MH, Nissenblatt M, Toppmeyer D, Moran MS. Breast cancer in young women (YBC): prevalence of *BRCA1/2* mutations and risk of secondary malignancies across diverse racial groups. *Ann Oncol*. 2009; 20(10):1653–1659.10.1093/annonc/ mdp051 [PubMed: 19491284]
 24. Young SR, Pilarski RT, Donenberg T, Shapiro C, Hammond LS, Miller J, Brooks KA, Cohen S, Tenenholz B, Desai D, Zandvakili I, Royer R, Li S, Narod SA. The prevalence of *BRCA1* mutations among young women with triple-negative breast cancer. *BMC Cancer*. 2009; 9:86.10.1186/1471-2407-9-86 [PubMed: 19298662]

Table 1

Subject characteristics

	All (<i>n</i> = 451) (%)	<i>BRCA1</i> (<i>n</i> = 27) (%)	<i>BRCA2</i> (<i>n</i> = 21) (%)	No founder mutation (<i>n</i> = 403) (%)
Age (mean)	57.1	45.5	54.8	58.1
Age <50	140 (31)	18 (67)	8 (38)	114 (28.3)
ER negative	99 (22)	22 (82)	7 (33)	70 (17)
PR negative	197 (44)	22 (82)	10 (48)	165 (41)
HER2 negative	388 (86)	25 (93)	18 (86)	345 (86)
TNBC	64 (14)	19 (70)	6 (29)	39 (10)

Table 2Association of “triple-negative” immunophenotype ($n = 64$) and mutation status by age

Age	Any mutation (%)	<i>BRCA1</i> mutation (%)	<i>BRCA2</i> mutation (%)
All ($n = 64$)	25/64 (39.1)	19/64 (29.7)	6/64 (9.4)
<50 ($n = 28$)	16/28 (57.1)	14/28 (50.0)	2/28 (7.1)
>50 ($n = 36$)	9/36 (25.0)	5/36 (13.9)	4/36 (11.1)

Table 3

Studies of germline BRCA1/2 mutation prevalence in TNBC

Study	BC cohort assessed	screening	BRCA1 prevalence	BRCA2 prevalence	TNBC Prevalence	BRCA1 prevalence among TNBC ^a	BRCA2 prevalence among TNBC ^a
Karp et al. [14]	149 Ashkenazi women <65 years old	BRCA1/2	11.4% (17/149)	2.7% (4/149)	30.9% (46 ^c /149)	28.2% (13/46 ^c)	0% (0/46)
Lidreau et al. [22]	70 Women <35	NA	9% (6/70)	NA	20% (14 ^b /70)	29% (4/14 ^b)	NA
Chang et al. [21]	76 Chinese women <45+ family history	BRCA1 alone	10.5% (8/76)	NA	56.2% (24 ^b /60)	25% (6/24 ^b)	NA
Atchely et al. [16]	491 women presenting for genetic testing	BRCA1/BRCA2	11.4% (56/491)	6.1% (30/491)	23.8% (93/391)	34.4% (32/93)	7.5% (7/93)
Foulkes et al. [13]	292 Ashkenazi women <65	BRCA1/BRCA2 ^d	10.6% (31/292)	NA	28% (76/268)	24% (17/72 ^c)	NA
Haffty et al. [23]	482 (only 99 BRCA-tested)	BRCA1/BRCA2 in 99 women	10% (10/99)	7% (7/99)	34% (34/99)	24% (8/34)	2.9% (1/34)
Young et al. [24]	54 women <40 with TNBC only	BRCA1/BRCA2	9.25% (5/54)	1.85% (1/54)	All (selected)	9.25% (5/54)	1.85% (1/54)
Gonzalez-Angulo et al. [12]	77 unselected TNBC	BRCA1/BRCA2	14.3% (11/77)	3.9% (3/77)	All (selected)	14.3% (11/77)	3.9% (3/77)
This study	451 Ashkenazi	BRCA1/BRCA2	6.0% (27/451)	4.7% (21/451)	14.2% (64/451)	29.7% (19/64)	9.4% (6/64)

^a In select cases, prevalence was evaluated in ER negative tumors with poor tumor differentiation instead of a triple-negative phenotype

^b ER negative tumors with poor differentiation

^c Only 72 patients with sufficient tissue for testing

^d All BRCA2 specimens discarded

^e ER negative status alone