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BRCA1/2 MUTATIONS AND TRIPLE NEGATIVE BREAST CANCERS

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Abstract

Identifying breast cancer patients at increased risk for carrying a mutation in the *BRCA1* and *BRCA2* genes is an important objective in clinical practice. Although age at diagnosis, family history of breast and/or ovarian cancer, and ethnicity are all essential parameters to consider when assessing risk, there are limitations as to how well such factors accurately predict *BRCA1/2* status, even when quantitative risk models are applied. Integrating information about triple negative (TN) disease may help refine these estimates. Among newly diagnosed breast cancer patients, fewer than 10% have a mutation in the *BRCA1* or *BRCA2* genes, and up to 20% present with TN disease. However, among *BRCA1* mutation carriers at least one-third have TN breast cancers. In this paper, we review key studies that have assessed breast cancer cases with a known *BRCA1/2* status and triple marker data. We also discuss how integrating such information into qualitative and quantitative risk assessments of *BRCA1/2* carrier probability may improve the ability to identify women who are appropriate candidates for genetic testing. Identifying women at increased risk is critical as knowledge of mutation status may impact surgical and systemic treatment in newly diagnosed patients, as well as recommendations for ovarian cancer risk management.

Keywords

BRCA1; *BRCA2*; genetic counseling; genetic testing; triple negative breast cancer; *BRCA* mutation prediction models; BRCAPRO

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INTRODUCTION

Approximately 5–10% of all newly diagnosed breast cancers in Western nations are hereditary, attributable primarily to inherited mutations in the *BRCA1* and *BRCA2* (*BRCA1/2*) genes. According to a recent meta-analysis, *BRCA1/2* gene mutations are associated with a 40–57% lifetime risk of female breast cancer and an 18–40% lifetime risk of ovarian cancer [10]. It is also well established that *BRCA1/2* carriers with breast cancer have markedly elevated risks of contralateral breast cancer of approximately 50% at 25 years post-diagnosis [21,22].

In general, management for mutation carriers with breast cancer includes consideration of risk reducing bilateral mastectomies or alternatively, breast cancer screening with annual mammography and magnetic resonance imaging (MRI) starting at age 25 years [37]. Bilateral salpingo-oophorectomy is recommended upon completion of childbearing not only to reduce ovarian cancer risk, but when performed premenopausally, it also reduces breast cancer risk, and has been shown to reduce mortality from both of these cancers [12,37].

Newly diagnosed breast cancer patients may take advantage of rapid genetic counseling and testing to inform surgical decisions if they test positive for a *BRCA1/2* mutation in that they may opt for bilateral mastectomies instead of breast conservation or unilateral mastectomy [41]. In addition, as reviewed by Rodler et al. in this volume, emerging data suggest that *BRCA1/2* carriers with TN disease may respond favorably to cisplatin-targeted therapy [6,8,42]. In addition, Poly(ADP-ribose) polymerase-1 (PARP-1) inhibitors appear to be particularly effective in *BRCA1/2* mutation carriers [44], and may also play a role in the treatment of sporadic TN disease [31]. Several ongoing trials of cisplatin and PARP inhibitors in *BRCA1/2* mutation carriers are currently in progress. In addition to the significant risks of developing cancer faced by probands (i.e., the first individual in a family to undergo genetic testing) with a positive test result, first-degree relatives of individuals with positive results have a 50% chance of inheriting the identified *BRCA1* or *BRCA2* mutation. Thus, the clinical and public health implications of identifying *BRCA1/2* mutation carriers are quite significant.

Potential candidates for *BRCA1/2* testing are typically identified based on a qualitative and/or quantitative analysis of personal and family history of cancer. However, given the limitations that may be encountered when interpreting a family history, increasing attention has been paid to whether breast cancer markers may provide an independent indication of women who are at increased risk of carrying a mutation. Specifically, the triple negative (TN) phenotype [i.e., defined by the absence of three markers: estrogen and progesterone receptors, and human epidermal growth factor (HER)-2 expression] is the most common histological subtype observed in *BRCA1* carriers. As described below, the prevalence of TN disease in *BRCA1* carriers is considerably higher than the general population prevalence of 11–20% [19].

It is important to note that many features of TN cancers overlap with those observed in basal-like cancers, but they are not identical [11]. While TN breast cancers are determined based on the assessment of the three key biomarkers mentioned above, basal-like cancers are defined based on gene expression assays and immunophenotypic profiles of cytokeratins. For the purposes of this review, we will focus primarily on TN breast cancers only, given that the pathologic markers used to determine this phenotype are routinely used in practice relative to cytokeratin studies, and therefore provide more accessible data for risk assessment.

TRIPLE NEGATIVE BREAST CANCER IN *BRCA1/2* MUTATION CARRIERS

Selection of studies

A literature review was performed to identify research studies reporting on the relationship between TN breast cancer and *BRCA1/2* carrier status. Studies were eligible for inclusion if the sample (or a subset of the sample) had a known *BRCA1/2* mutation status and pathology sufficient to evaluate TN status. Approximately 35 publications and abstracts were reviewed on the topic. Table 1 represents the 13 key studies which were selected for inclusion, three of which were abstracts.

Proportion of TN Breast Cancer by *BRCA1/2* Status

Excluding studies in which all cases had TN breast cancer, the proportion of TN breast cancer among *BRCA1* carriers ranged from 42–100%. The lower end of this range derived from the paper by Rakha et al. [39] is likely to be an underestimate given that some of the tumors acquired in that study were assessed for only two markers (ER and HER-2) and were negative; however, it is likely that many of these tumors were PR– as well, which would mean that up to 66% of the tumors in *BRCA1* carriers were TN. On the other hand, the proportion of TN breast cancer among known *BRCA2* carriers and *BRCA1/2* non-carriers both tended to be lower and more similar to each other (14–35% and 6–34%, respectively). Excluding studies that selected only TN breast cancers, the overall proportion of those that were TN was highest among *BRCA1* carriers, at 71%. The overall proportions of breast cancer cases that were TN among *BRCA2* carriers and *BRCA1/2* non-carriers were 25% and 17%, respectively.

Prevalence of *BRCA1/2* Carriers among TN Breast Cancer Cases

The prevalence of mutation carriers among patients with TN breast cancer is more variable than the TN prevalence among known carriers, as would be expected. In studies that calculated the prevalence of both *BRCA1* mutations and *BRCA2* mutations among TN breast cancer cases, the prevalence of *BRCA1* mutations was always higher. The proportion of *BRCA1* mutations among TN cases ranged from 9–100% (mean 35%), while the proportion of *BRCA2* mutations among TN cases ranged from 2–12% (mean 8%). The range among *BRCA1* carriers is wider than that for the *BRCA2* carriers; however, it is again important to consider outliers in this trend, which may be attributable to selection criteria of specific studies. For example, in the study by Young et al. (2009) [52], cases were selected based on age at breast cancer diagnosis only (i.e., age 40 or younger) with minimal family history. Thus, the number of *BRCA1/2* carriers is very low.

Considerations in Ascertainment

When assessing the relationship between *BRCA1/2* carrier status and TN disease, it is important to consider limitations in ascertainment criteria of the various studies. For example, two studies selected participants who were known *BRCA1/2* carriers [7,34], 3 studies selected patients from high risk clinics or based on a high prior probability of carrying a mutation [28,40,51], and 3 studies selected only participants with known TN breast cancer cases [18,26,52]. In 6 studies, *BRCA1/2* testing was performed prospectively [18,28,30,35,51,52]. Studies that included participants who underwent *BRCA1/2* testing because of established risk factors were more likely to have higher proportions of carriers, as one would expect. Fostira et al. [18] performed prospective testing regardless of risk level (i.e., unselected for family history, etc.), whereas the remaining 5 studies with prospective testing selected individuals for testing based on established risk factors (e.g., age at diagnosis and/or family history) [28,30,35,51,52]. Likewise, the 7 studies that assessed retrospective *BRCA1/2* test results had variable selection criteria. Consequently, this may

account for some variability in the proportion of *BRCA1* carriers among TN cases, as some individuals were more likely to test positive based on the presence of specific risk factors other than the tumor pathology. Moreover, in retrospective studies, in which patients were tested many years after their diagnosis, survivorship bias may affect prevalence rates. For example, if *BRCA1* carriers with TN disease had a higher rate of mortality relative to women with non-TN disease, then prevalence rates of carriers would be underestimated in the TN group and over-estimated in the non-TN group.

The majority of studies identified were in Caucasians; however, several studies were conducted in Chinese, various sub-populations of Caucasians (e.g., Ashkenazi Jewish), and in samples where race/ethnicity was not reported. The limited information regarding the relationship between TN breast cancer and *BRCA1/2* status in various ethnicities/races makes it difficult to assess for specific trends using this parameter.

Other limitations noted in some of the studies selected in this review include small sample sizes, variability in the extent of genetic testing performed, variability in how pathology was assessed, and absence of data on *BRCA1/2* non-carriers.

IDENTIFICATION OF *BRCA1/2* MUTATION CARRIERS

One of the challenges faced by clinicians is the identification of individuals for whom genetic testing is appropriate. Several key factors are used to aid in this process, including the age at diagnosis for the proband (e.g., breast cancer diagnosed < 50 years); ethnicity (e.g., presence of Ashkenazi Jewish ancestry); and family history, with the presence of epithelial ovarian cancer being a strong predictor of identifying a *BRCA1/2* mutation [17]. Increasingly, integration of breast cancer pathology, particularly TN status, is being used to refine estimates of *BRCA1* carrier probability.

Most genetic testing guidelines consist of criteria that include ethnicity as well as an individual's personal and family history of breast and genetically associated cancers, such as ovarian, prostate, and pancreatic [1,37,45]. However, as age of breast cancer diagnosis alone may be an indicator of hereditary risk, it is appropriate to offer *BRCA1/2* testing to young affected breast cancer patients even if they have no or minimal family history [37]. In many instances, though, these women will not test positive for *BRCA1/2* mutations [5,20,53]. In evaluating candidates for genetic testing, clinicians need to consider whether family history is limited or adequate enough to properly assess hereditary cancer risk [50].

Quantitative models are often useful adjuncts to qualitative pedigree interpretations to provide mathematical estimates of *BRCA1/2* carrier probability and associated *a priori* risks of breast and ovarian cancer, although such models have varying degrees of discriminatory accuracy [2,33,38]. Commonly used models in current clinical practice to assess probands with breast cancer include Myriad data [36], Penn II [47], BRCAPRO [4], BOADICEA [46], and Manchester [13,15]. These models vary in how they consider personal and family history of breast, ovarian, and other cancers; age at diagnosis of affected individuals; presence of and age of unaffected relatives; oophorectomy status; bilaterality of breast cancer; race/ethnicity; gene mutation penetrance; and contribution of genes other than *BRCA1/2* to hereditary breast cancer.

As mentioned, it is increasingly recognized that incorporating breast cancer pathology may improve *BRCA1/2* carrier risk prediction, particularly for breast cancer patients with less striking family histories. Specifically, the histopathology and immunohistochemistry of *BRCA1*-associated breast cancers may deviate in notable ways from patterns observed in sporadic (i.e., non-hereditary) cases [24]. Comparable to women with sporadic breast cancer, the most frequent histopathology in *BRCA1* mutation carriers is invasive ductal

adenocarcinoma; however, medullary carcinoma and atypical medullary carcinoma are over-represented in *BRCA1* carriers. As previously discussed, the tumors in *BRCA1* carriers are more frequently high grade and are negative for estrogen and progesterone receptors, and HER-2. Additionally, a high proportion of *BRCA1* tumors express basal markers such as the high molecular weight cytokeratins (CK), including CK5/6 and CK14 [24], although these markers are not currently routinely assessed in clinical practice. Conversely, studies have not demonstrated consistent findings regarding whether *BRCA2*-associated breast cancers exhibit a different histological profile relative to sporadic cases; however, they are more frequently moderately to poorly differentiated owing to less tubule formation, and have a higher proportion of continuous pushing margins [24]. Molecular profiles with regard to hormone receptor status, HER-2 protein expression, and basal markers in *BRCA2*-associated breast cancers appear to be similar to profiles observed in sporadic cases [24].

Thus, given the unique molecular phenotype noted in *BRCA1* carriers with breast cancer, in particular, the high prevalence of TN tumors, such information could be useful in improving *a priori* carrier prediction. Several studies have demonstrated that the use of tumor morphology, namely ER status and histological grade, can increase the sensitivity of *BRCA1* predictions even when family history is not considered [9,16,29,32]. Not surprisingly, more recent studies have shown that the inclusion of TN and basal markers is likely to be highly predictive of *BRCA1* status, particularly when basal markers are assessed in TN tumors [49].

Further, quantitative models have begun to integrate breast tumor markers in assessing *BRCA* carrier probabilities. Mavaddat et al. [34] used several tumor characteristics (e.g., receptor and triple negative status, basal markers) to improve the accuracy of BOADICEA. This modification is expected to become available on the BOADICEA web interface [34]. The Manchester scoring system was recently modified to include several pathological features, including grade 3 triple negativity, which significantly improved the model's ability to predict *BRCA1* status within a validation study [14]. The other model, which is the most widely used in the United States, BRCAPRO, considers positive or negative status for the following markers: ER, PR, and cytokeratins (CK5/6 and CK14) [43]. In a recent study, BRCAPRO outperformed five other models in selecting individuals for *BRCA1/2* mutation testing in clinical practice [25]. However, using tumor grade and hormone receptor status for an affected proband significantly improved the ability to discriminate *BRCA1* positive families, but not *BRCA2* positive families [25].

Finally, a recent Markov Monte Carlo simulation demonstrated that performing *BRCA1/2* testing in women with TN breast cancers diagnosed younger than age 50 is cost-effective, and if systematically applied in the U.S., could reduce the number of new breast cancers by 23% and reduce the number ovarian cancers by 41% [27]. The authors estimate that only 7–10% of unselected women with breast cancer will test positive for a *BRCA1* or *BRCA2* mutation, whereas up to 25% of women with TN breast cancer unselected for family history will test positive [27].

As an example of how consideration of TN status affects carrier probability, Figure 1 shows a hypothetical pedigree of a newly diagnosed breast cancer patient who presents for genetic counseling. She was diagnosed with breast cancer at age 40 and her mother was diagnosed with breast cancer at age 45. The pedigree was entered into CancerGene version 5.1 [48]. This computing platform includes the BRCAPRO model, which considers tumor pathology in addition to family history to calculate *BRCA1/2* carrier probabilities. As mentioned, the breast cancer tumor parameters that can be entered are ER, PR, CK5/6 and CK14 status (not tested/unknown, positive, or negative). Of note, the BRCAPRO model does not consider HER-2 status because it was not shown to be predictive of tumor marker status after accounting for ER [43]. When all markers are unknown, the proband's probability of testing

positive for a *BRCA1* or *BRCA2* mutation is only 3.6%. However, when her negative ER and PR status is entered, the carrier probability rises to 10.3% (i.e., 8.5% chance of a *BRCA1* mutation specifically), and when positive CK status for both markers is also included, her probability is a remarkable 50.6% (with most of that risk, 49.6%, accounting for a *BRCA1* mutation).

In summary, the integration of extensive tumor pathology including TN and basal markers appears to improve the ability to predict *BRCA1* carrier probability compared to standard risk factor analysis. In some cases, the resulting change in risk assessment with molecular markers could influence recommendations for genetic testing or the patient's decision to pursue genetic testing. It is also possible that consideration of molecular markers will become formally integrated into genetic testing criteria, including those used by insurance companies. However, it is important to note that at the present time, while markers for TN status are routinely assessed, CK markers are not.

SUMMARY

The ability to identify women at increased risk for carrying a *BRCA1* or *BRCA2* mutation remains an important priority for clinicians and researchers. In addition to traditional parameters used in risk assessment, such as age at cancer diagnosis, family history, and ethnicity, the addition of pathological markers often improves prediction of carrier probability. Specifically, the recognition that *BRCA1* carriers are more likely to develop TN breast cancers and express basal markers are important considerations in risk assessment, particularly for patients with less striking family histories. Quantitative models of *BRCA1/2* probability are increasingly integrating breast tumor pathology and are expected to undergo continued validation in the future. Once *BRCA1/2* mutation carriers are identified, management focuses on reducing the risk of breast and ovarian cancer, and extending genetic counseling and testing to interested at-risk relatives. Although knowledge of their *BRCA1/2* status may already influence surgical decision making in newly diagnosed breast cancer patients, such information may eventually play a more central role in systemic treatment decisions as well.

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FIG. 1.
Pedigree of newly diagnosed breast cancer patient

Characteristics of Key Studies Assessing Relationship between Triple Negative Breast Cancer and *BRCA1/2* Mutations

Table 1

First author, Publication year [reference]	Setting/Ascertainment criteria for <i>BRCA1/2</i> genotyping	Sample Characteristics				TN (n)/ <i>BRCA1</i> (n)	TN (n)/ <i>BRCA2</i> (n)	TN (n)/ <i>BRCA1/2</i> (n)	<i>BRCA1</i> (n)/TN (n)	<i>BRCA2</i> (n)/TN (n)
		Race/Ethnicity (%) ¹	TN (n)/eligible sample ² (n)	<i>BRCA1</i> (n), <i>BRCA2</i> (n)	<i>BRCA1/2</i> -(n)					
Fostira 2010[18] ³	Athens, Greece Unselected for age, FH; TN only	Greek/Caucasian	284/284 (100%)	30, n/a ⁴	254 ⁴	30/30 (100%)	n/a ⁴	254/254 (100%)	30/284 (11%)	n/a ⁴
Mavaddat 2010[34]	Cambridge, UK; BCLC Selected for <i>BRCA1/2</i> status	Caucasian	158/244 (65%)	182, 62	0 ⁷	143/182 (79%) ⁵	15/62 (24%) ⁵	n/a ⁶	143/158 (91%) ⁶	15/158 (9%) ⁶
Saura 2010[40] ³	Barcelona, Spain Selected via high risk clinic	Spanish/Caucasian	58/227 (26%)	20, 27	180	16/20 (80%)	5/27 (19%)	37/180 (21%)	16/58 (28%)	5/58 (9%)
Kwong 2009[28]	Hong Kong, China Selected via high risk clinic	Chinese	59/205 (29%) ⁷	12, 17 ⁷	176	8/12 (67%)	6/17 (35%)	45/176 (26%)	8/59 (14%)	6/59 (10%)
Rakha 2009[39]	Montreal, Quebec, Canada Selected for age (< 65) & ethnicity (AJ)	AJ/Caucasian	27/278 (10%)	30, n/a ⁴	248 ⁴	11/26 (42%) ⁸	n/a ⁴	16/248 (6%)	11/27 (41%)	n/a ⁴
Yip 2009[51]	Kuala Lumpur, Malaysia Selected for <i>BRCA1/2</i> risk level	Chinese (62%) Malays (26%) Indians (13%)	26/90 (29%)	10, 9	71	10/10 (100%)	3/9 (33%)	13/71 (18%)	10/26 (38%)	3/26 (12%)
Young 2009[52]	Various sites in USA Selected for age (< 40), minimal/no FH, & ethnicity (non-AJ); TN only	Caucasian (63%) AA (19%) Other (15%) Unspecified (4%)	54/54 (100%)	5, 1 ⁴	48 ⁴	5/5 (100%)	1/1 (100%)	48/48 (100%)	5/54 (9%)	1/54 (2%)
Atchley 2008[3]	Houston, TX, USA Selected for <i>BRCA1/2</i> status ⁹	Caucasian (72%) Hispanic (13%) AJ (9%) AA (4%) Asian (2%)	93/477 (19%)	56, 30	391	32/56 (57%)	7/30 (23%)	54/391 (14%)	32/93 (34%)	7/93 (8%)
Li 2008[30]	Various sites in China Selected for age (< 35) or positive FH	Chinese	17/78 (22%)	14, n/a ⁴	64 ⁴	7/14 (50%)	n/a ⁴	10/64 (16%)	7/17 (41%)	n/a ⁴
Byrski 2008[7]	Various sites in Poland Selected for age (early-onset)	Polish/Caucasian	22/34 (65%)	34, n/a ³	0 ³ ,6	22/34 (65%)	n/a ³	n/a ⁶	22/22 (100%) ⁶	n/a ³
Musolino 2007[35]	Parma, Italy Selected for age (<40)	Italian/Caucasian	19/45 (42%) ¹⁰	8, 3 ¹¹	35	7/8 (88%) ¹¹	1/3 (33%) ¹¹	12/35 (34%)	7/19 (37%)	1/19 (5%)
Haffty 2006[23]	New Haven, CT, USA Selected for <i>BRCA1/2</i> status	Caucasian (83%) AA (13%) Other (4%)	34/99 (34%)	10, 7	82	8/10 (80%)	1/7 (14%)	25/82 (30%)	8/34 (24%)	1/34 (3%)
Kandel 2006[26] ³	Boston, MA, USA; SPORE Selected for <i>BRCA1/2</i> status; TN only	Unspecified	23/23 (100%)	9, 2	12	9/9 (100%)	2/2 (100%)	12/12 (100%)	9/23 (39%)	2/23 (9%)

Abbreviations: ER-: estrogen receptor negative; PR-: progesterone receptor negative; HER-2 neg: human epidermal growth factor receptor 2 negative; TN: triple negative= ER-, PR-, and HER-2neg; *BRCA1*: *BRCA1* mutation carrier; *BRCA2*: *BRCA2* mutation carrier; *BRCA1/2* -: negative for mutations in these genes; FH: family history of breast and/or ovarian cancer; n/a: not applicable; BCLC: Breast Cancer Linkage Consortium; AJ: Ashkenazi Jewish; AA: African American; SPORE: Specialized Programs of Research Excellence

¹ Percentages may not add to 100% due to rounding

² Eligible sample = *BRCA* status known + pathology available to determine TN status

³ Abstract data only

⁴ Some participants had incomplete *BRCA1/2* testing (e.g. only *BRCA1*, only founder mutations, or *BRCA2* data not reported in original study)

⁵ TN proportions only calculated among cases known to be ER –

⁶ Sample consisted of known *BRCA1/2* carriers only

⁷ Eligible sample refers to number of tumors; includes 9 bilateral cases (4 *BRCA1*, 5 *BRCA2*)

⁸ This figure may be an underestimate. If the 19 *BRCA1* tumors that were ER– and HER-2 negative were also PR– (data not available), this proportion would be 19/29 or 66% (see table 3 in ref [39])

⁹ Original study excluded variants and double heterozygote from analysis

¹⁰ TN = ER–, PR–, HER-2 negative, and p53+

¹¹ Double heterozygote included with *BRCA1* and *BRCA2* carrier