Germline Mutations in Triple-Negative Breast Cancer

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Keywords

Triple-negative breast cancer · *BRCA1* · *BRCA2* · *PALB2* · *FANCM*

Summary

Triple-negative breast cancer (TNBC) is associated with a poor prognosis and defines a subgroup of patients who do not benefit from endocrine or anti-HER2 therapy. Rather than being a biological entity, TNBC represents a heterogeneous disease, and further subtyping is necessary to establish targeted therapies. Germline mutational status may serve as a robust biomarker predicting therapy response, especially with respect to compounds challenging the DNA repair machinery. Patients with TNBC usually show an early onset of the disease, as well as a positive family history of breast and/or ovarian cancer in more than one third of all cases, which suggests that TNBC is closely associated with a hereditary disease cause. In unselected TNBC cases, the prevalence of pathogenic germline *BRCA1/2* mutations is approximately twice as high as in breast cancer overall. Early age at diagnosis and positive family history are strong predictors for an increased *BRCA1/2* mutation probability, which is up to 40% when both risk factors are considered. Apart from *BRCA1/2*, the rarely mutated breast cancer predisposition genes *PALB2* and *FANCM* have been associated with TNBC. This review summarizes the role of germline mutational status in TNBC pathogenesis. Clinical trials addressing *BRCA1/2* mutation carriers are discussed.

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Introduction

The triple-negative breast cancer (TNBC) subtype is defined by a lack of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor type 2 (HER2; ERBB2) amplification/overexpression, and is associated with a poor prognosis [1–3]. The triple-negative tumor phenotype is reported to account for 12–24% of all breast cancers [1, 4], with comparatively high prevalences observed in patients with African-American ethnicity [5]. TNBC defines a relevant subgroup of patients who require targeted therapeutic strategies as they do not benefit from endocrine or anti-HER2 therapy [6]. Rather than being a biological entity, TNBC is a heterogeneous disease, and subtyping is necessary to establish molecular-based therapies [7]. Different subgroups of TNBC have been identified on the basis of protein expression, mRNA signatures, and genomic alterations, either on the somatic and/or the germline level [6, 8, 9]. Clinical trials of targeted therapies (e.g., immune checkpoint inhibitors, androgen receptor inhibitors, poly(ADP-ribose)polymerase (PARP) inhibitors, vascular endothelial growth factor receptor inhibitors) and platinum-based therapies in TNBC are ongoing, which have recently been reviewed in detail [6, 10, 11]. Notably, the TNBC phenotype appears to be closely associated with a hereditary cause of the disease [4]. This notion is based on i) the generally early age of onset which is similar to that observed for patients carrying germline mutations in breast cancer predisposition genes, ii) the high rate of TNBC cases with a positive family history of cancer, iii) the high prevalence of germline mutations, and, vice versa, iv) the association of a small subset of breast cancer predisposition genes (e.g., *BRCA1*, *BRCA2*, *PALB2*, *FANCM*) with the TNBC phenotype [12–15]. Most breast cancer predisposition genes, including *BRCA1/2*, are critical genes in the process of homologous recombination (HR) repair of double-strand DNA breaks [13, 16–19]. Heterozygous germline inactivation of HR genes may be accom-

panied by a somatic inactivation of the second allele, resulting in a HR deficiency and limited DNA repair capacities of the tumor cells [20]. There is increasing evidence that breast cancers arising in *BRCA1/2* germline mutation carriers are associated with a better response to DNA-damaging treatment regimens [17, 21–25]. Thus, this short review aims to summarize the role of germline mutational status in TNBC pathogenesis, which may serve as a robust biomarker predicting therapy response, especially with respect to DNA-damaging compounds.

TNBC Phenotype Associated with Early Disease Onset

According to the National Cancer Institute (NIH) and the Robert Koch Institute (RKI), the overall mean age at first diagnosis for breast cancer is 62–64 years. In contrast, in unselected TNBC patients, the mean age at first diagnosis is considerably earlier, with reports ranging from 51 to 58 years [2, 26–31]. For Germany, the Munich Cancer Registry (www.tumorregister-muenchen.de/en/facts/base/bC50f_E-ICD-10-C50-Breast-cancer-women-incidence-and-mortality.pdf) reported a TNBC phenotype in 8.6% of all breast cancers and in 19.8% of breast cancer cases with an age at onset before 40 years [32]. These data confirm a generally early disease onset for TNBC patients, an observation which is assumed to be driven by genetic predisposition. For example, breast cancer patients carrying pathogenic *BRCA1* or *BRCA2* germline mutations show a mean age of onset of 40 and 43 years [33], respectively, and patients carrying pathogenic *PALB2* mutations have a mean age of onset of 53 years [14].

TNBC and Family History

In a large targeted sequencing study of mainly Caucasian TNBC patients, a positive family history was reported in 539 of 1,510 (35.7%) unselected TNBC cases [26]. In this study, family history was defined as positive when at least 1 first- or second-degree relative was affected by breast cancer or ovarian cancer. In a cohort of unselected Hispanic women with TNBC, 56 of 146 (38.4%) reported breast cancer in first- or second-degree relatives [34]. Concordant results were shown in an investigation of 207 unselected TNBC patients with different ethnicities [27]. In this study, a family history of breast or ovarian cancer was reported in 76 of 207 (36.7%) cases, with a positive family history being defined as ≥ 1 close blood relative (first-, second- or third-degree) with breast cancer at age ≤ 50 years, or ≥ 1 close blood relative with ovarian cancer [27]. Apart from the different ethnicities and the slightly different definitions of a positive family history applied in these studies, there is compelling evidence that more than one-third of all TNBC patients have a familial background of breast and/or ovarian cancer when first- and second-degree relatives are taken into account.

Elevated Prevalence of *BRCA1/2* Mutations in TNBC

While germline *BRCA1/2* mutations are found in 5.3% of unselected breast cancers according to The Cancer Genome Atlas [28], a study by Couch et al. [26] showed that 11.2% of unselected TNBC cases had deleterious mutations in the *BRCA1* (8.5%) and *BRCA2* (2.7%) gene, respectively. Of note, TNBC patients with mutations showed a younger age at first diagnosis and had higher-grade tumors than those without mutations [26]. A mean age at first diagnosis of 44 and 47 years was reported for TNBC patients with *BRCA1* and *BRCA2* mutations, respectively, while TNBC patients without pathogenic germline mutations show a mean age at first diagnosis of 51 years. In summary, even TNBC cases unselected for a positive family history of cancer and/or early disease onset appear to be enriched for deleterious germline mutations in *BRCA1/2*. In other studies, the *BRCA1/2* mutation frequencies of unselected TNBC patients vary between 9.4 and 18.2% (table 1) [26, 27, 29–31, 35–37].

High Prevalence of *BRCA1/2* Mutations in Early-Onset and/or Familial TNBC

When stratified by family history, the study by Couch et al. [26] revealed that 66 of 539 (12.2%) TNBC patients with a family history of cancer carry pathogenic *BRCA1/2* mutations, compared to 83 of 969 (8.6%) patients without a family history of cancer. More pronounced differences were observed when stratified by disease onset. A total of 78 of 386 (20.2%) *BRCA1/2* mutation carriers were observed in the subgroup of TNBC patients with a disease onset before age 40 compared to 94 of 1,122 (8.4%) patients with a disease onset $\geq$ age 40. Similar differences were observed in the GeparSixto trial (NCT01426880) [38]. In this study, 31 *BRCA1/2* mutation carriers were observed among 110 (28.2%) TNBC patients with a positive family history of cancer compared to only 19 of 181 (10.5%) patients without a positive family history of cancer. In the subgroup of patients with a disease onset before age 40, 23 of 65 (35.4%) were shown to carry a pathogenic *BRCA1/2* gene mutation compared to 27 of 226 (11.9%) patients with a disease onset $\geq$ age 40. Similarly, an investigation of a genetic counseling cohort revealed a 43.8% (64/146) prevalence of *BRCA1/2* mutation carriers among TNBC patients with an age at first diagnosis of < 40 years [39]. Thus, *BRCA1/2* mutation frequencies appear to be generally high in early-onset and/or familial TNBC cases. The inclusion criteria of the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC) for genetic *BRCA1/2* testing consider both, family history and disease onset (table 2). According to the data generated by the GC-HBOC as of November 2016, a total of 16,979 breast cancer index patients with known receptor status fulfill these criteria, of which 3,234 (19%) carry pathogenic *BRCA1/2* mutations. Among these 16,979 familial index cases, 3,662 (21.6%) patients with a TNBC tumor phenotype were observed (mean age at onset: 42.7 years), of which 1,254 (34.2%) carried pathogenic *BRCA1* and 174 (4.8%) pathogenic *BRCA2* alterations, clearly demonstrating that the cohort of early-onset/familial TNBC is enriched for *BRCA1/2* mutation carriers.

Table 1. *BRCA1/2* mutation prevalences in triple-negative breast cancer (TNBC) patients not selected for age at first diagnosis or family history of breast and/or ovarian cancer

TNBC cases (unselected), n	Proportion <i>BRCA1</i> positive, n (%)	Proportion <i>BRCA2</i> positive, n (%)	Proportion <i>BRCA1/2</i> positive, n (%)	Reference
77	11 (14.3)	3 (3.9)	14 (18.2)	[29]
199	13 (6.5)	8 (4.0)	21 (10.6)	[30]
990	71 (7.2) ^a	22 (2.2) ^a	93 (9.4) ^a	[35]
1,824	155 (8.5) ^a	49 (2.7) ^a	204 (11.2) ^a	[26]
291	43 (14.7)	7 (2.4)	50 (17.1)	[36]
105	13 (12.4)	2 (1.9)	15 (14.3)	[37]
774	44 (5.7) ^a	30 (3.9) ^a	74 (9.9) ^a	[31]
207	23 (11.1) ^b	9 (4.3) ^b	32 (15.5) ^b	[27]

^aStudy does not cover larger deletions/duplications (copy number variations, CNVs) within the *BRCA1/2* genes.

^bOnly a subset of patients was screened for CNVs. According to a GeparSixto investigation, pathogenic CNVs in the *BRCA1/2* genes were found in approximately 1.7% of unselected TNBC patients [36].

Still a Matter of Debate: Germline *BRCA1/2* Testing in Sporadic TNBC Patients

According to the National Institute for Health and Care Excellence (NICE), genetic *BRCA1/2* testing is recommended when the combined *BRCA1* and *BRCA2* mutation carrier probability is $\geq 10\%$ [27]. Given the comparatively high *BRCA1/2* mutation frequency even in unselected TNBC cases, an incorporation of the TNBC subtype in guidelines for genetic testing is discussed. According to the National Comprehensive Cancer Network and the American Society of Breast Surgeons, *BRCA1/2* testing is generally recommended for women with TNBC diagnosed at age ≤ 60 years, irrespective of a positive cancer family history [27]. However, the age-dependent *BRCA1/2* mutation carrier probability was largely unknown for TNBC patients without family history, and the data presented by Couch et al. [26] suggests a *BRCA1/2* mutation carrier probability below the recommended 10% threshold in sporadic TNBC cases with an age at first diagnosis of < 60 years. Our recent *BRCA1/2* germline analysis of 802 TNBC patients without a family history of breast and/or ovarian cancer suggests that the *BRCA1/2* mutation prevalence exceeds the threshold of 10% in sporadic TNBC patients with an age at diagnosis of < 50 years (manuscript in preparation) [32]. However, the confidence interval in the group with an age at first diagnosis of 40–49 years requires confirmation. The finding that a subgroup of *BRCA1/2*-positive patients with TNBC do not show a positive family history may be explained by disease modifiers that are independent from *BRCA1/2* [4], de novo mutations, or limited family structures.

Other Predisposition Genes Associated with TNBC Phenotype

Many of the other genes involved in HR repair are now recognized to also contribute to hereditary breast and/or ovarian cancer risk, including *ATM*, *BRIP1*, *CHEK2*, *NBN*, *PALB2*, *RAD51C*, and *RAD51D*, while only limited evidence is available for *BARD1*, *FANCM*, *MRE11A*, and *RAD50* [13, 15, 17–19, 40]. Notably, only

Table 2. ‘Positive family history’ as defined by the inclusion criteria of the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC) for *BRCA1* and *BRCA2* germline testing

≥ 3 women with breast cancer
≥ 2 women with breast cancer, 1 with onset below 51 years of age
≥ 1 woman with breast cancer and 1 woman with ovarian cancer
≥ 2 women with ovarian cancer
≥ 1 woman with breast- and ovarian cancer
≥ 1 woman with breast cancer below 36 years of age
≥ 1 woman with bilateral breast cancer with onset below 51 years
≥ 1 male with breast cancer and 1 woman with breast or ovarian cancer

BRCA1, *BRCA2*, *PALB2*, and *FANCM* have so far been associated with the TNBC phenotype [12–15]: Approximately 66–70% of breast cancers arising in *BRCA1* mutation carriers and up to 16–23% of breast cancers in *BRCA2* carriers are triple-negative [35, 41]. A recent analysis of patients positive for *PALB2* germline mutations revealed 34% being triple-negative. For *FANCM*, higher mutation frequencies were observed in TNBC cases versus breast cancer cases not selected for tumor phenotype [13, 15]. Other breast cancer risk genes such as *CHEK2* and probably *ATM* are unlikely to predispose for TNBC [42]. With the rise of next generation sequencing, germline testing is nowadays not restricted to *BRCA1/2* and covers the above-named and further genes that predispose for rare cancer predisposition syndromes [40]. Besides *BRCA1/2*, the study by Couch et al. [26] analyzed 15 ‘non-*BRCA1/2*’ cancer predisposition genes (i.e., *ATM*, *BARD1*, *BRIP1*, *CDH1*, *CHEK2*, *MRE11A*, *NBN*, *PALB2*, *PTEN*, *RAD50*, *RAD51C*, *RAD51D*, *STK11*, *TP53*, *XRCC2*). Deleterious mutations in non-*BRCA1/2* genes were detected in only 3.7% of unselected TNBC patients, while *PALB2* mutations prevailed (21/1,828; 1.1%).

Germline Mutation Status as Biomarker for Therapy Response

Approximately 9–18% of unselected TNBCs and up to 40% of the early-onset and/or familial TNBC cases may be explained by

germline mutations in *BRCA1*, *BRCA2* and, to a much smaller extent, *PALB2* and possibly other risk genes. There is increasing evidence that breast and also ovarian cancers arising in *BRCA1* and *BRCA2* germline mutation carriers are attributed to a better response to DNA-damaging treatment regimens [17, 21–24], including PARP inhibitors [23]. The PARP inhibitor olaparib is currently under investigation in *BRCA1/2* germline mutation carriers with HER2-negative primary breast cancer (Olympia study, NCT02032823). Favorable response rates to DNA-damaging compounds are also likely for patients carrying germline mutations in other predisposition genes intimately involved in HR repair, as recently shown for ovarian carcinomas [25]. Thus, mutational status might be considered as a valuable biomarker to predict therapy response also in TNBC. In a neoadjuvant trial, it was shown that platinum-based chemotherapy is highly effective in *BRCA1* germline mutation carriers, i.e., 61% of 82 TNBC patients experienced a pathologic complete response (pCR) following cisplatin single-agent therapy [21]. The high sensitivity of *BRCA1/2* mutation carriers to platinum-based chemotherapy [21] is in line with data in the metastatic or recurrent locally advanced setting where carbop-

latin monotherapy revealed significantly higher response rates in *BRCA1/2* mutation carriers compared with patients without *BRCA1/2* mutations [43]. The GeparSixto trial revealed that germline *BRCA1/2* mutation status predicts higher pCR rates after neoadjuvant anthracycline/taxane-based chemotherapy in TNBC. Given the fact that germline testing in TNBC patients is widely recommended even in the absence of a positive family history, the germline mutation status might be easily available and should implicitly be considered for clinical management.

Acknowledgement

This work was supported by German Cancer Aid (No. 110837).

Disclosure Statement

EH, KR, and RKS received honoraria for scientific advisory board meetings from Astra Zeneca. The other authors declared no conflicts of interest.

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