Clinicopathological characteristics and treatment response in South African breast cancer patients screened for actionable gene variants involved in DNA repair: a public sector experience

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Abstract

Introduction: Hereditary breast carcinomas have unique characteristics, but tumor-associated information specifically for mutation carriers is lacking for South Africa (SA). As pathology-supported genetic testing integrates traditional pathology findings with genomics for application of personalized medicine, this pilot study aimed to inspect the clinicopathology of breast tumours and related treatment responses among genetically characterized patients, representative of the SA population.

Material and Methods: This retrospective descriptive study (UFS-HSD2024/2460/2907) investigated a consecutive series of breast cancer (BC) cases diagnostically tested at the National Health Laboratory Service (NHLS) in Bloemfontein between 2021 and 2024. Genetic, immunohistochemistry (IHC), and histopathology results were retrieved from the NHLS TrakCare LabView information system. Inclusion criteria entailed: i) screened using the 15-gene Oncomine™ BRCA expanded Research Assay; ii) being affected with primary BC, and iii) female sex. Mutation carriers of actionable variants in genes not involved in the sensing and recognition of DNA repair (such as *BRCA2*) were excluded from this investigation.

Results

Of the 1,458 BC patients included, infiltrating ductal carcinoma (IDC) was the most common (80.9%), with a smaller proportion (4.3%) of invasive lobular cancer (ILC) identified. Contrary to the literature, high-grade papillary carcinoma was observed (average 43.7 years), with most exhibiting lymph node metastasis. Despite IDC with a medullary pattern having a good prognosis, the average age at onset was earlier (42.2 years), with most presenting with high-grade stage III carcinomas with advanced lymph node involvement. Most patients with ILC reported a family history and were affected with bilateral disease. No associations were observed between ER-PR-HER2- tumours and their aggressiveness in Black African patients, with most diagnosed with hormone receptor-positive cancer. Most patients presented with late-stage tumours at first diagnosis and opted for unilateral mastectomies together with either an axillary clearance or a sentinel lymph node biopsy, with 28% including contralateral preventive surgery. Genotype–phenotype correlation revealed a high occurrence of *HER2*-positive or equivocal tumours among *BRCA1* mutation carriers. *CHEK2*-associated tumours tend to be hormone receptor-positive, exhibiting a high-grade *in-situ* solid component in ~50% of cases. Pathological staging in *CHEK2*-mutation carriers indicated aggressive disease, with 70% already at stage III at the time of testing. Despite surgical intervention, these patients did not respond well to neoadjuvant therapy.

Conclusions

Our findings indicate a delay in seeking medical care among Black African and Indian BC patients, as evidenced by presentation with advanced BC (stages III to IV) at first diagnosis. The use of fluorescence *in situ* hybridisation (FISH) to further classify IHC 2+ equivocal cases among patients with pathogenic *BRCA1* variants, typically associated with triple-negative breast cancer, may reflect limited access to anti-HER2 therapy in the public sector. Although this observational study lacks the capacity for generalizing the results to the SA population at large, we highlighted the need to consider both tumour pathology and germline mutation status to optimise surgical decision-making, presymptomatic diagnosis of at-risk family members, and use of targeted therapies such as PARP inhibitors in the future.