Demographics and Clinical Decision Making in Patients with Germline Moderate Penetrance non-BRCA Mutations in Breast Cancer Related Genes

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Background: There are numerous risk factors that affect breast cancer (BC) incidence and mortality, including, but not limited to, age, race, income, insurance status, reproductive patterns, breast density, and germline genetic mutations. Approximately 10% of BC cases are thought to be hereditary, with pathogenic mutations in high penetrance genes such as *BRCA1* and *BRCA2* being well studied. However, moderate penetrance mutations are under studied. In this study, we aim to compare risk reduction decision making patterns in patients without a prior BC diagnosis who are found to have a moderate penetrance BC-related genetic mutation.

Methods: Female patients age 18+ who tested positive for a pathogenic or likely pathogenic *BRCA1/2* or moderate penetrance mutation related to BC between 1996 and 2023 were selected from a single academic center's database. Groups were stratified by mutation type (*BRCA1/2* versus moderate penetrance mutation) and BC risk management (prophylactic mastectomy vs no mastectomy). Relevant germline genetic mutations were defined as *BRCA1/2* mutations (*BRCA1*, *BRCA2*) or moderate penetrance mutations (*ATM, BARD1, CHEK2, NF1, RAD51C, RAD51D*). Surveillance was defined as patients who did not undergo mastectomy. Demographics and clinical outcomes were compared between groups.

Results: A total of 438 patients were included in the study, with 69% (n=304) of patients having a *BRCA1/2* mutation and 31% (n=134) having a moderate penetrance mutation; the median follow-up was 3.7 years. The median age at genetic testing was 42 years old (IQR 31-52) in the *BRCA1/2* cohort and 47 years old (IQR 37-60) in the moderate penetrance cohort ($p<0.001$). Most patients opted for surveillance in both cohorts (*BRCA1/2* 80.9% vs moderate penetrance 92.5%), although some underwent mastectomy in both cohorts (*BRCA1/2* 19.1% vs moderate penetrance 7.5%) and management varied during the follow-up period.

Compared to the *BRCA1/2* cohort, patients with moderate penetrance mutations were more likely to be married/partnered and have private insurance (both $p<0.05$). Patients in the moderate penetrance cohort were also more likely to choose surveillance, less likely to have a family history of BC and were less likely to have a subsequent diagnosis of malignancy (all $p<0.05$). Within the moderate penetrance cohort, patients who chose to undergo prophylactic mastectomies were younger at the time of genetic testing and tended to have a higher number of family members with BC. In patients with moderate penetrance mutations, no association was found between the decision to undergo prophylactic mastectomy and race/ethnicity, sexual orientation, marital status, insurance status, smoking status, contraceptive use, or BMI.

Conclusions: We found notable differences in the age, marital status, and insurance type of patients without a history of or concurrent BC who were found to have a germline moderate penetrance mutation in a BC-related gene compared to those with a *BRCA1/2* mutation. Additionally, we found associations between age at the time of genetic testing and number of family members with BC, and the decision to undergo prophylactic mastectomies in patients with moderate penetrance mutations. Our findings provide useful insights into the demographic makeup of patients with moderate penetrance mutations and those who pursue prophylactic surgery.