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Breast Cancer Risk in MSH6 And MSH2 Role in Lynch Syndrome Female Patients: A Single Institution Retrospective Analysis

Short Commentary

Lynch syndrome (LS) is a germ pathogenic mutations involving DNA Mismatch Repair (MMR) genes: LS is linked with the development of MMR-deficient (MMRd) cancers and is associated with an increased risk of several malignancies including gastrointestinal, genitourinary, gynecologic, skin, and brain cancers.

Despite immense advancement in the knowledge available regarding molecular basis of breast cancer development, no biomarker is used in disease management except BRCA1 and BRCA2.

Human MSH6 protein is one of the most important mismatch repair proteins in the post-replicative DNA mismatch repair system (MMR)'s and plays a core role in repairing mismatched DNA bases in the process of DNA mismatch binding dissociation, the encoded protein can heterodimerize with MSH2 to form mismatch recognition complex, and exchange ADP and ATP as bidirectional molecular switch.

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Functioning of mismatch repair proteins involves 2 central dimers MutLα (MLH1 and/or PMS2) and MutSα (MSH2 and/or MSH6). Intact MSH2 and MLH1 are compulsory to maintain the stability of MSH6 and PMS2 respectively. However, MLH1 and MSH2 stability can be maintained in the absence of MSH6 or PMS2 because role is compensated by other mismatch repair proteins. Therefore, expression analysis of particular proteins by immunohistochemistry can lead to precise estimation of affected mismatch repair deficiency [1-2].

Breast cancer is treated with hormonal therapy, anticancer drugs, radiotherapy, and surgery. It was reported that loss of mismatch repair activity manifests cells resistant to various chemotherapeutic agents like 5-fluorouracil, cisplatin, topoisomerase inhibitors, and alkylating agents. Mismatch repair deficient phenotype may be developed during chemotherapeutic treatment. Therefore, literature is lacking in the field weather mismatch repair deficiency is responsible for breast cancer development or mismatch repair deficient phenotype is a result of any chemotherapeutic agent.

So whether patients with LS have higher risk of developing breast cancer (BC) or not is a relevant clinical question. From the Santa Maria alle Scotte Hospital registry, we retrospectively identified female patients with LS diagnosed showed by the detection of a germ heterozygous pathogenic or likely-pathogenic variant in MLH1, MSH2, MSH6 or PMS2 on molecular genetic testing within April 2017 to June2025. We compared our sample size to SEER of 2017 NCI database.

Overall, 50 female patients with LS were identified. Of those, 13 (26%) had primary BC (95% CI 1.463% to 26.7189% Chi-squared 5.95 p<0.0001). Among the BC LS patients, 91% (12) have a hormone receptor positive tumor and BC is the only diagnosis of cancer to date. 7 patients (45%) with BC LS have germinal MSH6 mutation, 4 of 13 patient has MSH2 alteration. MSH2 and MS6 patients have a more aggressive breast cancer with local relapse disease and distant metastases. Median age at diagnosis is 54.5 years, median follow up is 8 years: All patients are still alive and under treatment

In our single institution analysis, 26 % of female patients with LS developed BC. Our study suggests that MSH6 and MH2mutations are closely linked to the occurrence, progression and metastasis of breast cancer. Further investigation with prospective clinical studies with larger samples is warranted to validate our data.

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