Non-breast cancer related germline mutations in breast cancer patients: A single institution experience.

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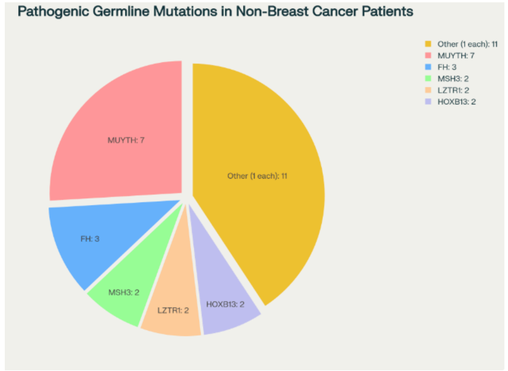
Background

- Breast cancer is the most common non-cutaneous malignancy among women, with around 10% of cases involving germline mutations in DNA repair genes.
- Germline mutations in the BRCA1/2 genes significantly increase breast cancer risk. Other relevant genes to increase the risk of breast cancer include TP53, PTEN, PALB2, CHEK2, and ATM.
- Multigene panel testing can sequence many genes, sometimes identifying non-disease-related genes and variants of unknown significance.

Methods

- We reviewed patients with newly diagnosed breast cancer diagnosis from 2022 to 2024 in our institution.
- Germline genetic testing was offered to all newly diagnosed breast cancer patients at the time of diagnosis irrespective of their family history. Testing was offered to patients with invasive breast cancer and ductal carcinoma in situ.
- The goal of this study was to identify the prevalence of genes not attributed to increasing the risk of breast cancer and the implications of those results.

Conclusions



Breast Cancer Subtype & Marker	Percentage of Patients
Invasive Ductal Carcinoma (IDC	66
Ductal Carcinoma In Situ (DCIS)	18
Estrogen Receptor (ER) Positive	81
HER2-Positive (overall)	14
HER2-Low (subset of HER2-positive)	62

- We present our single institution's experience of germline mutations in breast cancer patients.
- Previously, we observed CHEK2 being the most common breast cancer-related germline mutation in our patient population. This analysis focuses on identifying germline mutations without an increased risk of breast cancer. MUTYH was the most common pathogenic mutation identified.
- Further studies are needed to determine the actual risk percentage of breast cancer associated with the MUTYH gene. Universal testing for all breast cancer patients is feasible with the lower cost of multi-gene panels.
- However, identifying other non-disease-related genes, as observed in our study, has implications. Patients must be informed about the consequences of a positive result, including genetic counselling, additional screening tests, and testing of immediate family members.

Results

- A total of 478 patients (Invasive cancer and DCIS) were seen in our oncology clinic from January 2022 to December 2024. The median age at diagnosis was 66 years (range 28-91).
- Invasive ductal cancer (IDC) was the most common subtype (66%), followed by DCIS (18%). Most patients had estrogen-positive cancer (81%), and approximately 14% had HER2-positive disease (62% HER2 low).
- We found 27 patients with pathogenic germline mutations which are not related to breast cancer risk. The most common mutation was MUYTH (7 patients), followed by the FH gene (3 patients). MSH3, LZTR1, and HOXB13 genes were each found in 2 patients. APC, BAP1, BLM, BRIP1, NTHL1, SDHA, SDHB, MSH6, MITF, and FLCN genes were each identified in one patient.
- All patients with MUYTH mutations had hormone-positive (HER2-negative) disease, contrary to the limited observation of triple-negative breast cancer related to the MUYTH gene in the available literature.
- Patients with positive mutations were offered genetic counselling and referred to a high-risk genetics clinic. FANCM was observed in one patient, who has rarely been associated with an increased risk of triple-negative breast cancer.

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