ID# 581461 CLINICAL AND PATHOLOGICAL FEATURES OF BREAST CANCER AMONG MEN AND WOMEN WITH ATM AND CDH1 PATHOGENIC VARIANTS

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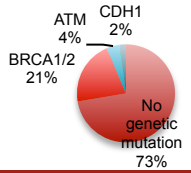
Introduction

Multigene panel testing for hereditary breast cancer has facilitated the identification of variants in cancer susceptibility genes other than BRCA1/2. We identify men with pathogenic variants (PV) in breast cancer susceptibility genes other than BRCA1/2 after breast cancer (BC) diagnosis and compare their clinical and pathological features to women with the same PV.

Methods

The Stanford Clinical Cancer Genetics Research Database was queried for men with breast cancer (MBC) who underwent genetic testing. Based on the PV other than BRCA1/2 identified in MBC, we then queried the database for women with breast cancer (WBC) carrying those same variants. All patients gave informed consent for participation in an IRB-approved research protocol. Clinical data and histopathology were analyzed from patient records. 95% confidence intervals (CI) were calculated for proportions.

Men with Breast Cancer (MBC)

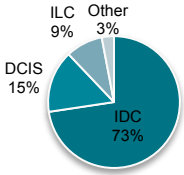


Results

Clinical features of men and women with ATM and CDH1-associated breast cancer				
NonBRCA1/2 mutation (n= total patients)	ATM (30)		CDH1 (5)	
Gender, variable (n=number of tumors)	Female (n=31)	Male (n=2)	Female (n=4)	Male (n=1)
Median age at diagnosis	45.5	48.5	48.5	80
Initial presentation: % patients (95% CI)				
Abnormal self-breast exam	53.6 (35.8, 70.5)	100 (29, 100)	50 (15, 85)	100 (16.8, 100)
Screen-detected breast cancer	39.3 (23.5, 57.3)	0 (0, 71.0)	50 (15, 85)	0 (0, 83.3)
Mean tumor size (cm ± SEM)*	2.2 ± 0.36	2.9 ± 0.9	4 ± 1.6	1.4
Lymph node disease (% known cases)**	31 (17.1, 49.4)	50 (9.5, 90.6)	25 (3.4, 71.1)	0 (0, 83.3)
Primary surgery (n=patients)				
Unilateral mastectomy	6	1	--	1
Bilateral mastectomies	7	--	4	--
Breast conservation	15	1	--	--

*Tumor size determined by final pathology after surgery including tumor bed size after neoadjuvant chemotherapy treated cases. Largest span measurement used. SEM=standard error of the mean. **One unknown case.

Histopathology of ATM–associated breast cancer



ATM-associated tumors	n=33
ER+/HER2-	19
ER+/HER2 untested	7
ER+/HER2+	5
ER-/HER2+	1
ER-/HER2 untested	1

There were no ATM or CDH1-associated triple negative breast cancers as can be seen in carriers of pathogenic variants in BRCA1.

By comparison, all 5 **CDH1 pathogenic variant carriers** with BC had ER+/PR+/HER2- invasive lobular carcinoma, including the male CDH1 PV carrier. Two female patients developed signet ring cell gastric adenocarcinoma after their BC diagnosis and underwent total gastrectomy, while the male carrier had a prior history of colorectal and prostate cancer.

Double Pathogenic Variant Carriers

Three women had an additional PV in CHEK2, one of whom developed an ipsilateral breast recurrence. Another had a PV in BRCA2. 75% [95% CI, 28.9%-96.6%] of the double PV carriers presented with Stage III disease and were younger at diagnosis (median age 36.5).

Conclusions

- Similar to nonhereditary BC, the majority of men and women with ATM-associated breast tumors have hormone receptor-positive IDC.
- Those with a second pathogenic variant present nearly a decade earlier than those with a single mutation and with more advanced disease.
- Men with CDH1 PV may present with invasive lobular carcinoma of the breast, similar to female CDH1 PV carriers, which is otherwise extremely rare in men.

Future Directions

As multigene panel testing becomes the standard of care in the treatment plan for breast cancer patients, we need to gain a better understanding of the penetrance, and the predictive and prognostic value of inherited pathogenic variants in cancer susceptibility genes in order to better counsel our patients and their families. Male breast cancer is under-studied and more work is needed to understand the contribution of inherited pathogenic variants in cancer susceptibility genes and the phenotype and outcomes of associated cancers.

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