Germline Findings in Breast Cancer Genes: Initial Results from the WISDOM Study

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Background

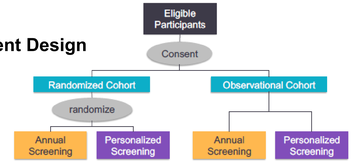
WISDOM (Women Informed to Screen Depending on Measures of Risk) is pragmatic, randomized-controlled trial with a preference-tolerant observational arm comparing annual screening mammography to personalized, risk-based breast cancer (BC) screening.

Women aged 40-74 years with no personal history of breast cancer or DCIS and no prior double mastectomy are eligible to participate. Recruitment was done through targeted efforts at various health systems, health insurance carriers, and employers, and nationally through wisdomstudy.org. The purpose of this analysis is to describe the initial germline and family history findings of the risk-based participants in the WISDOM study.

Methods

Participants in the risk-based arm underwent germline testing (next-generation sequencing and deletion/duplication analysis of *ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, STK11, TP53*) and completed a baseline questionnaire that included self-reported family history of cancer, race/ethnicity, and personal and family genetic testing history. Participants in the risk-based group (via randomization into personalized screening or participant-selected personalized screening in the observational arm) that had a test report issued through the study were included in this analysis. (Figure 1).

Figure 1: Study Enrollment Design



Results

Of 17,377 participants with reported germline testing at censoring, 541 (3.1%) individuals had at least 1 pathogenic or likely pathogenic variant (PV/LPV) identified.

Mutation carriers were distributed as demonstrated in Table 1. 8 participants were identified with two PV/LPVs: all had *CHEK2*, with *ATM* (2), *BRCA2* (2), *CHEK2* (2), and *PALB2* (2).

The average age of mutation carriers was 54.3yrs vs 54.2yrs in non-mutation carriers.

The WISDOM study identified a pathogenic or likely pathogenic variant (PV/LPV) in 3.1% of participants undergoing germline testing for 9 genes.

- **Of PV/LPV carriers, 14.8% were previously known, reported by the participant, and concordant with testing.**
- **The majority of PV/LPVs were identified in CHEK2 (1.61%), ATM (0.52%), and BRCA2 (0.48%).**
- **A substantial proportion of PV/LPV carriers reported no family history of breast cancer in first or second-degree relatives (24%-46%).**

Table 1: Germline Results Distribution

	#	%
CHEK2	279	1.61
ATM	91	0.52
BRCA2	83	0.48
BRCA1	50	0.29
PALB2	30	0.17
TP53	5	0.03
CDH1	2	0.01
STK11	1	0.01
PTEN	0	-
TOTAL	541	3.1

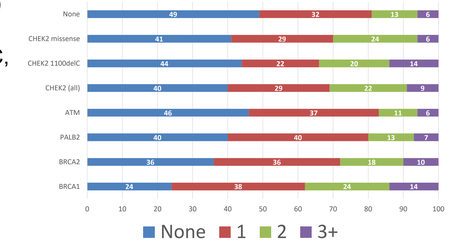
Learn more about the WISDOM study:
https://www.thewisdomstudy.org/

Results Continued

Of mutation carriers, 177/535 (33%) reported a first-degree relative (mother, sister, or daughter) with BC, compared to 4489/16,845 (27%) in those with a negative germline test result.

Of those with PV/LPV in a common high or moderate penetrance gene, the proportion of participants that reported a first or second degree relative (F/SDR) with breast cancer ranged from 54% (*ATM+*) to 76% (*BRCA1+*) compared to 52% in those with a negative germline test result (Figure 1).

Fig. 2: Proportion of participants reporting family history (and number) of first- or second-degree relatives with breast cancer



In this cohort, 24-46% of PV/LPV carriers report no family history of breast cancer in a F/SDR, compared to 49% in non-mutation carriers.

2,680 participants in the germline testing cohort (15.4%) endorsed Jewish ancestry, of which 114 (4.3%) were identified with a PV/LPV: 27 Jewish BRCA1/2 founders, 45 CHEK2 S428F, and 42 other.

1,384 participants (8%) reported having prior germline testing. Of these, 131 (9.5%) reported testing positive for mutation.109 named a specific gene, of which only 80 (14.8% of all PV/LPV carriers) were confirmed on germline testing on the 9-gene panel.

Discussion

Wisdom participants are enriched for having a close relative with breast cancer, reflected in the relatively high rate of CHEK2 and ATM mutations. Notably mutation carriers report a close relative with breast cancer at similar rates to non mutation carriers. Mutations in syndromic genes were rare. These results may help inform the development of future germline testing strategies for inherited breast cancer risk in an unselected population.

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