Inherited Germline Mutations in Men with Prostate Cancer

Virginia Cancer Specialists

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BACKGROUND

- There is a high prevalence of pathogenic variants in genes that confer hereditary cancer risk among men with metastatic prostate cancer.
- Currently, prostate cancer is not regarded as an indication for genetic testing.

OBJECTIVE

- We evaluated genetic testing with a multi-gene hereditary cancer panel among men with a personal history of prostate cancer.

METHODS

COHORT

- Men with prostate cancer who underwent testing with a multi-gene hereditary cancer panel between September 2013 and December 2017 were included in this analysis.
- Clinical information was obtained from provider-completed test request forms.
- Approximately 75% of tests were ordered by Genetics, Medical Oncology, Urology, or Hematology/Oncology providers.

GENETIC TESTING

- The multi gene panel included *APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, GREM1, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, SMAD4, STK11,* and *TP53.*
- All genes were available for the full testing period, except *POLD1, POLE,* and *GREM1,* which were added in July 2016.
- Pathogenic variants were those that received a laboratory classification of Deleterious or Suspected Deleterious.

ANALYSIS

- Individuals with a history of only prostate cancer were evaluated separately from those who had a personal history of one or more additional cancers.

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RESULTS

- 1,240 men with a personal history of prostate cancer were tested with the hereditary cancer panel in this 4-year period.
  - 794 (64.0%) men had a history of only prostate cancer.
  - 446 (36.0%) men had a history of prostate cancer and at least 1 additional cancer.

Table 1. Cancer history among men with prostate cancer and ≥1 additional cancer (n=446)

Additional Cancer	N	% of Patients*
Colon Cancer	150	33.6%
Breast Cancer	142	31.8%
Melanoma	60	13.5%
Pancreatic Cancer	35	7.8%
Gastric Cancer	13	2.9%
Other Cancer	170	38.1%

*115 individuals have >1 cancer diagnoses in addition to prostate cancer (106 with 2 additional malignancies, and 9 with 3 additional malignancies).

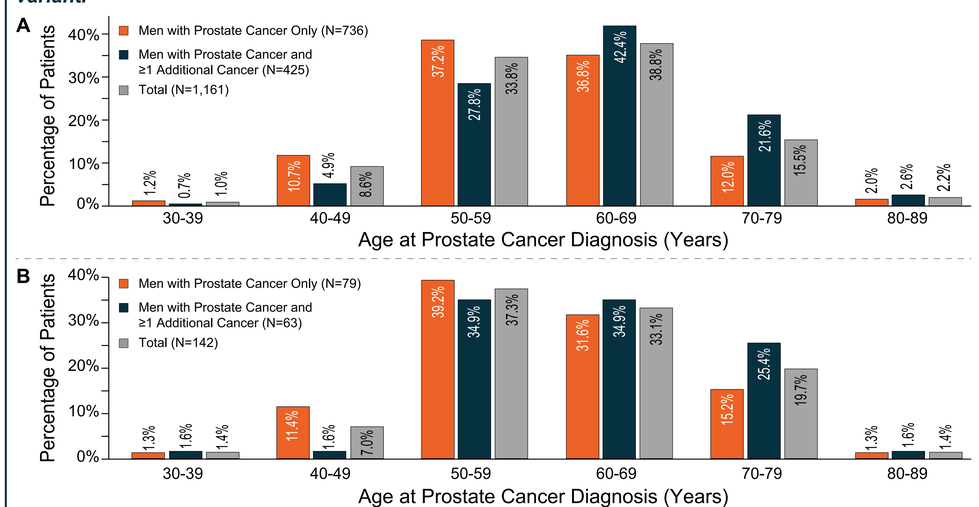
- The most common additional cancers among men with prostate and another cancer(s) were colon and breast cancer (Table 1).
- The mean age of prostate cancer diagnosis was 60.9 (Table 2), compared to 66 for all men with prostate cancer (SEER data 2009-2013).
- There were only slight differences in the age at diagnosis between men who had prostate cancer only and those with additional cancer history (Table 2, Figure 1A).

Table 2. Age at prostate cancer (PC) diagnosis

	PC Only	PC + Additional Cancer(s)	Total*
N	737	425	1,162
Mean (SD)	59.6 (9.13)	63.0 (8.80)	60.9 (9.16)
Range	34, ≥90	35,86	34, ≥90

*78 individuals missing age of diagnosis are not included here (57 with PC only and 21 with PC plus another malignancy).

Figure 1. Age at prostate cancer diagnosis among A) all men tested and B) men with a pathogenic variant.



78 individuals missing age of diagnosis (57 with only prostate cancer, 21 with prostate and another cancer) and 1 individual diagnosed >90 are not included here.
4 individuals with multiple pathogenic variants in different genes excluded (1 with prostate cancer only, 3 with prostate and another cancer).

- Overall, 12.1% of men with prostate cancer were found to carry one or more pathogenic variants in the genes tested here (Table 3).
  - The positive rate was significantly higher among men with a personal history of prostate and another cancer(s) (14.7%) compared to men with only prostate cancer (10.6%, p=0.035).

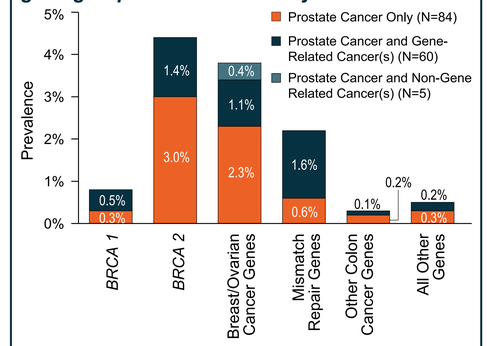
Table 3. Prevalence and gene distribution of pathogenic variants among men with prostate cancer (PC)

Gene	PC Only	PC + Additional Cancer(s)	Total*
BRCA1 and BRCA2			
BRCA1	4 (0.5%)	6 (1.4%)	10 (0.8%)
BRCA2	37 (4.7%)	17 (3.8%)	54 (4.4%)
Genes Associated with Breast/Ovarian Cancer			
ATM	11 (1.4%)	7 (1.6%)	18 (1.5%)
BARD1	1 (0.1%)	0	1 (0.1%)
BRIP1	4 (0.5%)	0	4 (0.3%)
CHEK2	10 (1.3%)	12 (2.7%)	22 (1.8%)
NBN	1 (0.1%)	0	1 (0.1%)
PALB2	1 (0.1%)	0	1 (0.1%)
RAD51C	1 (0.1%)	0	1 (0.1%)
Mismatch Repair Genes			
MLH1	0	6 (1.4%)	6 (0.5%)
MSH2	2 (0.3%)	11 (2.5%)	13 (1.1%)
MSH6	2 (0.3%)	2 (0.5%)	4 (0.3%)
PMS2	3 (0.4%)	1 (0.2%)	4 (0.3%)
Other Genes Associated with Colon Cancer			
APC	2 (0.3%)	1 (0.2%)	3 (0.2%)
MUTYH	1 (0.1%)	0	1 (0.1%)
Other Genes			
CDH1	1 (0.1%)	0	1 (0.1%)
CDKN2A	1 (0.1%)	0	1 (0.1%)
PTEN	1 (0.1%)	0	1 (0.1%)
TP53	1 (0.1%)	2 (0.5%)	3 (0.2%)
Total	84 (10.6%)	65 (14.7%)	149 (12.1%)

*Patients with a PV in >1 gene are excluded: PC only (*BRCA2* & CHEK2); PC + other (ATM & *CDKN2A*, *ATM* & *PMS2*, *BRCA2* & *CHEK2*).

- Most men with a pathogenic variant were diagnosed between the ages of 50 and 69, regardless of whether additional cancer history was present (Figure 1B).
- The prevalence of pathogenic variants in *BRCA2* was higher among individuals with only prostate cancer (Figure 2).
- The prevalence of MMR mutations was higher among individuals with additional cancer history, most of whom also had cancers associated with Lynch syndrome (Figure 2).

Figure 2. Prevalence of pathogenic variants by gene group and cancer history



Gene Group (See Table 3)

4 individuals with multiple pathogenic variants excluded (1 with prostate cancer only, 3 with prostate and another cancer)

CONCLUSIONS

- Overall, approximately 12% of men with prostate cancer in this cohort had a pathogenic variant in a cancer-risk gene.
- This included genes with a well known prostate-cancer risk (i.e. *BRCA2*) as well as genes associated with other cancers, including breast and colon.
- This suggests that hereditary cancer testing in men with prostate cancer may aid in medical management decision making to reduce overall cancer risk.

PLEASE EMAIL ROBERT REID (ROBERT.REID@USONCOLOGY.COM) WITH ANY QUESTIONS OR COMMENTS