Exploration of Germline Mutation Burden in a Hereditary Cancer Panel Cohort Identifies Gaps in Cancer Risk Associations and Testing and Management Guidelines

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BACKGROUND & METHODS

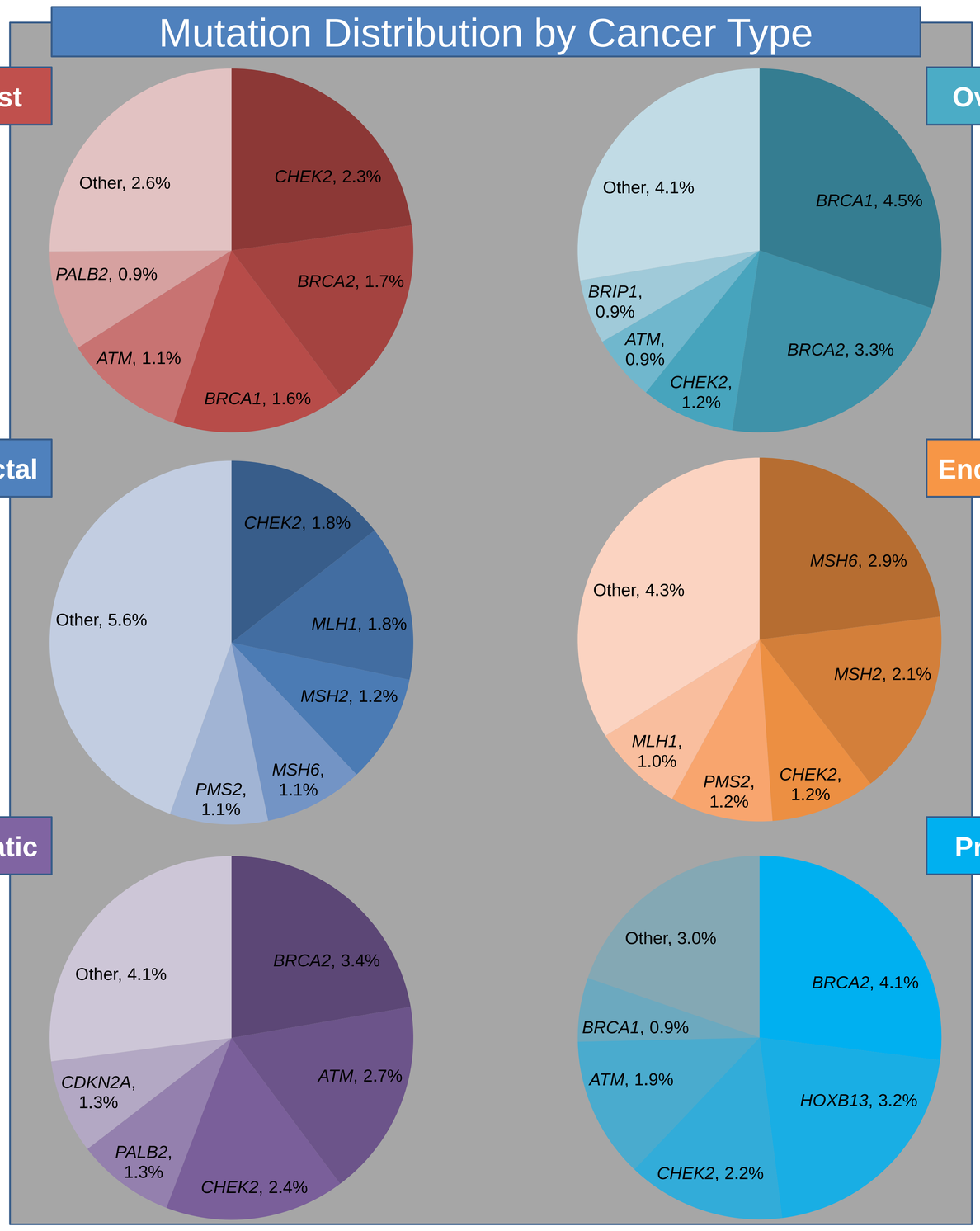
- With increased utilization of hereditary cancer multigene panel testing (MGPT), independent efforts have explored yield and utility for various testing indications.
- Few systematic approaches have used this data to further our understanding of cancer risk associations and support modifications to current testing and management guidelines.
- We explored mutation frequency by cancer type in patients with a single primary breast (female), colorectal (nonpolyposis), ovarian, endometrial, pancreatic, or prostate cancer selected from a cohort of >175,000 cases referred for hereditary cancer MGPT (5-49 genes).
- Pathogenic/likely pathogenic variant frequencies were calculated for 32 genes known to predispose to at least one of the six cancer types:
  - *APC,ATM,BARD1,BMPR1A,BRCA1,BRCA2,BRIP1,CDH1,CDKN2A,CHEK2,EPCAM, GREM1,HOXB13,MLH1,MRE11A,MSH2,MSH6,MUTYH,NBN,NF1,PALB2,PMS2, POLD1,POLE,PTEN,RAD50,RAD51C,RAD51D,SMAD4,SMARCA4,STK11,TP53*
- The availability of cancer-specific risk estimates, management guidelines, and testing guidelines was assessed in the five most frequently mutated genes for each cancer type.

DEMOGRAPHICS

Cancer site	Total n	Gender		Median Age at Testing (years)	Ethnicity					
		Female n (%)	Male n (%)		Caucasian n (%)	Ashkenazi Jewish n (%)	African American n (%)	Asian n (%)	Hispanic n (%)	Other/ Unknown n (%)
Breast (female)	68,212	68,212 (100.0)	0 (0.0)	51	42,543 (62.4)	3471 (5.1)	5423 (8.0)	3449 (5.1)	4422 (6.5)	8904 (13.1)
Ovarian	9308	9308 (100.0)	0 (0.0)	61	6573 (70.6)	353 (3.8)	360 (3.9)	490 (5.3)	483 (5.2)	1049 (11.3)
Colorectal	6037	3468 (57.4)	2569 (42.6)	47	3939 (65.2)	194 (3.2)	423 (7.0)	255 (4.2)	420 (7.0)	806 (13.4)
Endometrial	2376	2376 (100.0)	0 (0.0)	57	1601 (67.4)	131 (5.5)	86 (3.6)	94 (4.0)	159 (6.7)	305 (12.8)
Pancreatic	1368	730 (53.4)	638 (46.6)	60	861 (62.9)	139 (10.2)	72 (5.3)	45 (3.3)	67 (4.9)	184 (13.5)
Prostate	476	0 (0.0)	476 (100.0)	64	318 (66.8)	65 (13.7)	23 (4.8)	6 (1.3)	13 (2.7)	51 (10.7)

Cancer Risks, Management Recommendations, and Testing Guidelines For Frequently Mutated Genes by Cancer Type

Mutation Distribution by Cancer Type



Breast

Gene	Published Cancer Risk	Guidelines	
		Management	Testing
CHEK2	2.3-fold[1]	YES[5]	NO
BRCA2	45-84%[2,3]	YES[5]	YES[5]
BRCA1	57-87%[2,4]	YES[5]	YES[5]
ATM	2.8-fold[1]	YES[5]	NO
PALB2	7.5-fold[1]	YES[5]	NO

Ovarian

Gene	Published Cancer Risk	Guidelines	
		Management	Testing
BRCA1	40%[2]	YES[5]	YES[5]
BRCA2	11-18%[2,6]	YES[5]	YES[5]
CHEK2	Not increased[7]	NO	NO
ATM	2.3-fold[7]	NO	NO
BRIP1	5.0-fold[7]	YES[5]	NO

Colorectal

Gene	Published Cancer Risk	Guidelines	
		Management	Testing
CHEK2	2.1-fold[8]	YES[9]	NO
MLH1	52-82%[9]	YES[9]	YES[9]
MSH2	52-82%[9]	YES[9]	YES[9]
MSH6	10-22%[9]	YES[9]	YES[9]
PMS2	15-20%[9]	YES[9]	YES[9]

Endometrial

Gene	Published Cancer Risk	Guidelines	
		Management	Testing
MSH6	16-26%[9]	YES[9]	YES[9]
MSH2	25-60%[9]	YES[9]	YES[9]
CHEK2	Not well defined	NO	NO
PMS2	15%[9]	YES[9]	YES[9]
MLH1	25-60%[9]	YES[9]	YES[9]

Pancreatic

Gene	Published Cancer Risk	Guidelines	
		Management	Testing
BRCA2	Not well defined	YES[12]	YES[5,12]
ATM	Not well defined	YES[12]	YES[12]
CHEK2	Not well defined	NO	NO
PALB2	Not well defined	YES[12]	YES[12]
CDKN2A	17-25%[10,11]	YES[12]	YES[12]

Prostate

Gene	Published Cancer Risk	Guidelines	
		Management	Testing
BRCA2	15%[13]	YES[5]	YES[5]
HOXB13	Not well defined	NO	NO
CHEK2	2.2-fold[14]	NO	NO
ATM	Not well defined	NO	NO
BRCA1	Not well defined	YES[5]	YES[5]

SUMMARY

Research efforts aimed at generating precise cancer risk estimates and improved testing and management recommendations for more commonly mutated genes will have the largest immediate impact for counseling patients and their families, including:

1. Further integration of *ATM*, *CHEK2*, and *PALB2* into hereditary cancer testing guidelines.
2. Defining cancer risks and management recommendations for *CHEK2* carriers beyond breast and colorectal cancer.
3. Defining risk, management, and testing guidelines for hereditary prostate and pancreatic cancers (beyond familial pancreatic cancer).

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