Comparison of Cancer Risks in Truncating versus Missense Pathogenic *CHEK2* Variants

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BACKGROUND

- *CHEK2* associated cancer risk estimates are based mainly on studies of the most common pathogenic truncating variant, c.1100del.
- Lack of information regarding cancer risks in non-truncating *CHEK2* pathogenic variants leaves uncertainty for individuals with these variants, especially for those with missense variants.
- This uncertainty can raise questions about appropriate screening and management recommendations.
- Here we compared personal and family cancer histories of individuals with pathogenic *CHEK2* truncating and missense variants.

METHODS

Cohort

- Individuals who had pan-cancer panel genetic testing between September 2013 and October 2017 were assessed.
- Variants with a classification of Suspected Deleterious or Deleterious were considered pathogenic.

Analysis

- Individuals carrying a single truncating or missense pathogenic variant in the *CHEK2* gene were included for analysis.
- Clinical and ancestry information was obtained from healthcare provider completed test request forms.
- Personal and family (first and second degree relatives) cancer histories were evaluated based on variant type.
- Chi-square tests were used to compare cancer prevalence according to variant type. P-values less than 0.05 were considered significant.

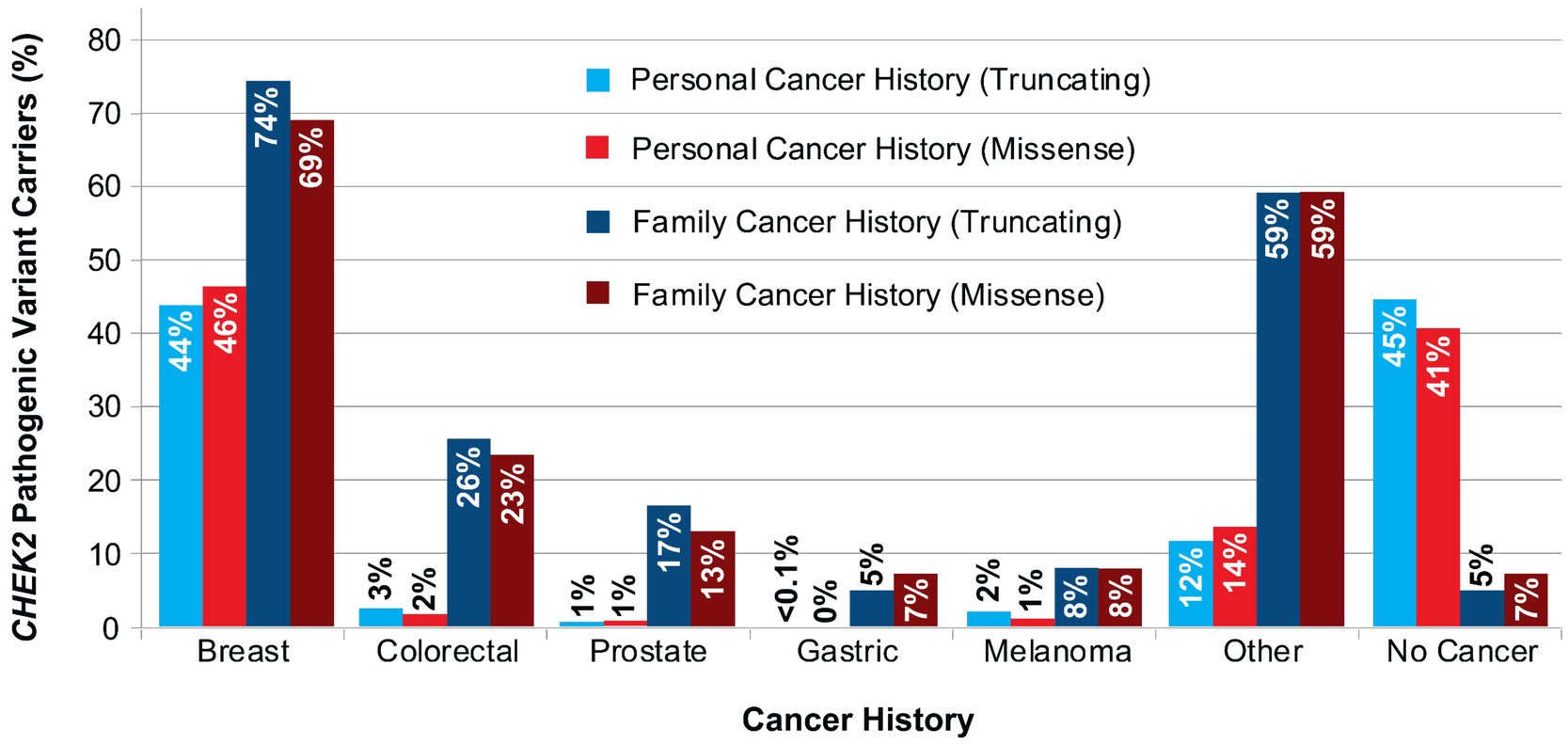
RESULTS

- 3,368 individuals with a single truncating or missense pathogenic *CHEK2* variant were identified.
  - 2,650 (78.7%) individuals had a truncating variant and 718 (21.3%) individuals had a missense variant.
- There were no significant differences in personal cancer history among individuals with truncating or missense pathogenic *CHEK2* variants (Figure 1).
- There was also no evidence of significant differences in age of diagnosis.
  - Median age at first breast cancer diagnosis was 48 for individuals with truncating variants and 47 for individuals with missense variants.
- There were slight differences in family history of breast ($p<0.01$), prostate ($p=0.02$) and gastric ($p=0.02$) cancer based on variant type (Figure 1).

Table 1. Self-Reported Ancestry of Individuals with *CHEK2* Pathogenic Variants

Ancestry	Truncating	Missense
Ashkenazi Jewish	23 (0.9%)	1 (0.1%)
Asian	7 (0.3%)	3 (0.4%)
Black/African	31 (1.2%)	6 (0.8%)
Hispanic/Latino	39 (1.5%)	159 (22.1%)
Middle Eastern	9 (0.3%)	1 (0.1%)
Native American	34 (1.3%)	7 (1.0%)
White Non-Hispanic	1,736 (65.5%)	365 (50.8%)
Other	11 (0.4%)	1 (0.1%)
Multiple Ancestries	155 (5.8%)	40 (5.6%)
None Specified	605 (22.8%)	135 (18.8%)

Figure 1. Comparison of Personal and Family Cancer History by Variant Type



CONCLUSION

- Cancer risk estimates for truncating *CHEK2* pathogenic variants, such as c.1100del, appear to be applicable to pathogenic missense variants.

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