CANCER PREVALENCE IN MSH3 HETEROZYGOTES

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BACKGROUND: Biallelic pathogenic and likely pathogenic variants in *MSH3* are associated with *MSH3*-related polyposis and colorectal cancer. However, observations of *MSH3* heterozygotes with early-onset colorectal cancers (CRC) and/or polyposis raise questions of possible cancer associations. In prior studies, no increased CRC risk was observed in *MSH3* heterozygotes; however, these studies are limited by small sample size or variant annotation that depends on *in-silico* tools and imputation.

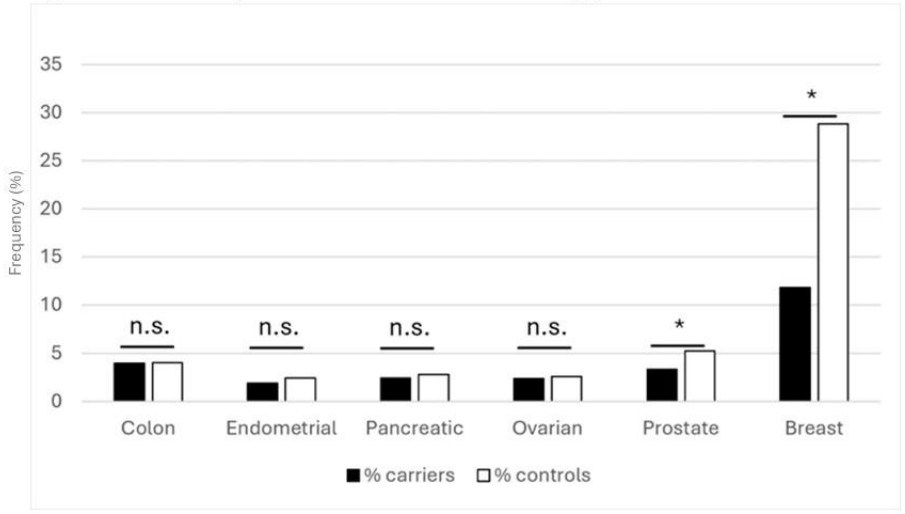
METHODS: We retrospectively analyzed the prevalence of colorectal and other tumors in confirmed *MSH3* heterozygotes (n=1,317) identified from a large pan-cancer multigene panel testing (MGPT, between 2018-2024) cohort. Tumor phenotypes were inferred through ICD-10 codes, validated for high sensitivity and specificity. Using Fisher's exact test, the prevalence of reported tumors in *MSH3* heterozygotes were compared to genotypically negative individuals (n=102,858) that had pan-cancer MGPT (70+ genes).

RESULTS: The prevalence of CRC in *MSH3* heterozygotes was 3.95% compared to 4.03% in the negative cohort (OR=0.977, 95% CI 0.725-1.292, p=.94). Additionally, the prevalence of endometrial cancer in *MSH3* heterozygotes was 1.90% compared to 2.41% in the negative cohort (OR=0.78, 95% CI 0.503-1.162 p=.27). Additional cancers such as ovarian (2.35% vs 2.57%) and pancreatic (2.43% vs 2.82%), showed no statistically significant difference compared to the control group, with breast (11.85% vs 28.82%) and prostate (3.34% vs 5.22%) showing a statistical negative association.

CONCLUSIONS: These data show no significant enrichment of colorectal, endometrial, ovarian, or pancreatic cancers in *MSH3* heterozygotes compared to a large, similarly ascertained negative MGPT cohort. Breast and pancreatic cancer show a negative association; however, this may reveal test order or other bias rather than a protective effect. Proactive assessment with thorough phenotype curation in larger cohorts is warranted to fully assess *MSH3*-related disease risks. This study adds to the growing body of evidence showing no cancer predisposition in MSH3 heterozygotes, providing important information for clinical management.

Keywords: colorectal cancer, polyposis, MSH3, autosomal recessive inheritance

Figure 1. Cancer prevalence in *MSH3* heterozygotes



*=p<.01; n.s.= not significant

Table 1. Odds of cancers in *MSH3* heterozygotes compared to genotype negative controls

	Heterozygotes N (%) of 1,317	Controls N (%) of 102,858	OR	95%CI	P value
Colon	52 (3.95)	4,152 (4.04)	0.977	0.725 to 1.292	p= .943
Endometrial	25 (1.89)	2,485 (2.42)	0.782	0.503 to 1.162	p= .276
Pancreatic	32 (2.43)	2,905 (2.82)	0.857	0.582 to 1.219	p= .450
Ovarian	31 (2.35)	2,647 (2.57)	0.913	0.616 to 1.305	p= .725
Prostate	44 (3.34)	5,370 (5.22)	0.627	0.453 to 0.849	p= .0017
Breast	156 (11.85)	29,650 (28.83)	0.332	0.279 to 0.393	p < .0001