COLORECTAL CANCER PREVALENCE IN *MSH3* HETEROZYGOTES

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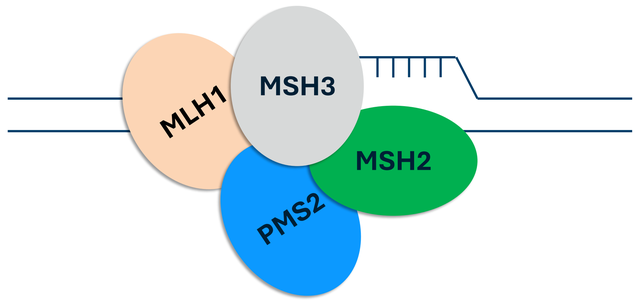
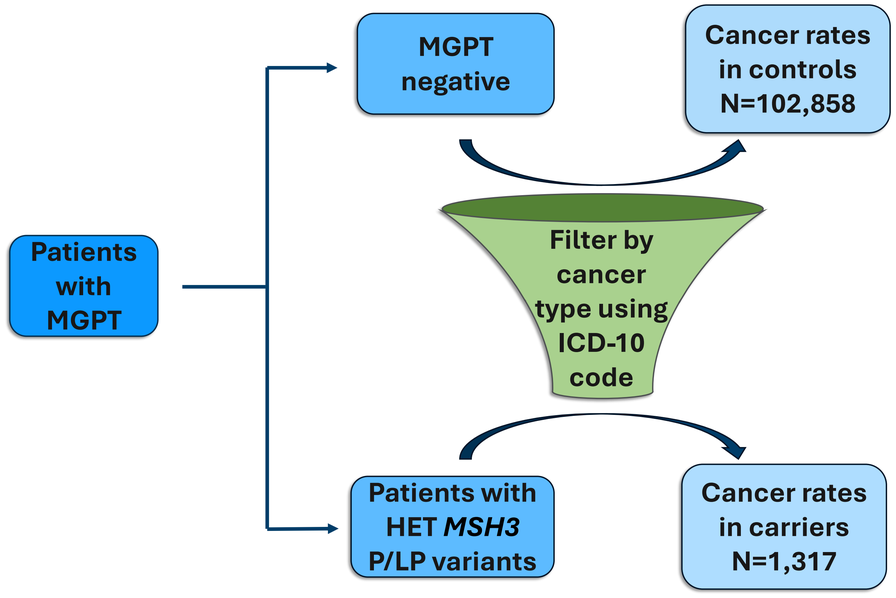
BACKGROUND

- Biallelic pathogenic variants in *MSH3* are associated with *MSH3*-related polyposis and colorectal cancer.
- MSH3 heterodimerizes with MSH2 to recognize multi-nucleotide mismatches, triggering mismatch repair (below).
- While *MSH3* is recognized as an AR disorder, anecdotal observations of early onset polyps and CRC in heterozygous carriers continue to raise questions about whether heterozygotes are at increased cancer risk.



METHODS

- Retrospective assessment of cancer prevalence in confirmed pathogenic *MSH3* heterozygotes who received multigene panel testing (MGPT) between 2018 and 2024.
- Affected status was determined by the ICD-10 code reported on patient test order forms.
- Heterozygous individuals were compared against a similarly ascertained negative cohort using Fisher's exact test.



RESULTS

Figure 1

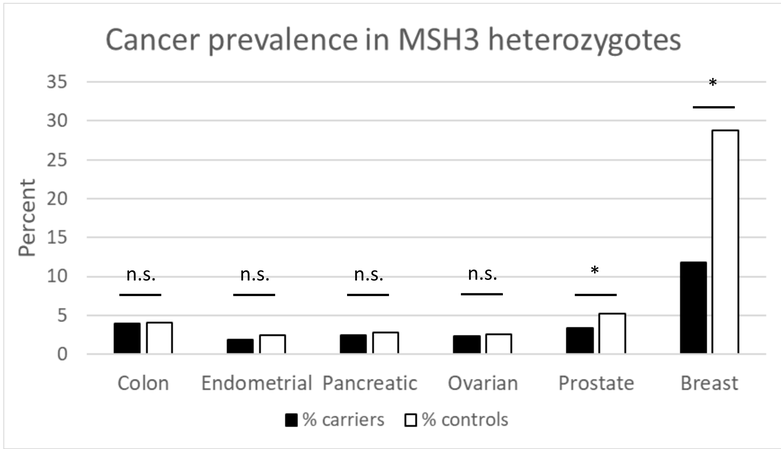


Table 1. Odds of cancer in *MSH3* HET compared to wild-type control cohort

	HET N (%) of 1317	Controls N (%) of 102858	OR	95% CI	p value
Colon	52 (3.95)	4152 (4.04)	0.977	0.725 to 1.292	p= .943
Endometrial	25 (1.89)	2485 (2.42)	0.782	0.503 to 1.162	p= .276
Pancreatic	32 (2.43)	2905 (2.82)	0.857	0.582 to 1.219	p= .450
Ovarian	31 (2.35)	2647 (2.57)	0.913	0.616 to 1.305	p= .725
Prostate	44 (3.34)	5370 (5.22)	0.627	0.453 to 0.849	p= .0017
Breast	156 (11.85)	29650 (28.83)	0.332	0.279 to 0.393	p < .0001

Figure 1 and Table 1. Cancer prevalence in *MSH3* HET. Low odds ratios suggest no clear evidence for elevated risk of colon, endometrial, pancreatic or ovarian cancers in individuals carrying a single HET pathogenic or likely pathogenic *MSH3* variant. There is a lower rate and risk of breast and prostate cancer patients in *MSH3* carriers compared to controls.

LIMITATIONS

- One of the major features of *MSH3*-related polyposis is colonic polyps. These are historically difficult to capture on test requisition forms, so affected individuals may not be completely represented.

TAKE HOME POINTS

- There is no significant association of *MSH3* carrier status with colorectal cancer, endometrial cancer, ovarian cancer or prostate cancer.
- Breast and prostate cancers show a negative association, but these could be due to ascertainment bias rather than a protective effect. Possibly including higher rates of reflex testing for breast cancer patients to larger panels including *MSH3*.
- These data suggest that there is no autosomal dominant cancer predisposition in individuals with pathogenic or likely pathogenic heterozygous variants in *MSH3*.