Title: Breast and colorectal cancer risk in monoallelic *MUTYH* carriers ascertained via multi-gene panel testing

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Background: Whether monoallelic *MUTYH* mutation carriers are at increased risk of breast cancer (BC) and/or colorectal cancer (CRC) remains controversial. We aimed to determine whether monoallelic *MUTYH* mutations are associated with increased BC and/or CRC risk by comparing the frequency of *MUTYH* mutations among BC and CRC cases to controls from a multi-gene panel testing (MGPT) cohort.
Methods: Cases included Caucasian individuals with female BC (N=16,921; 349 *MUTYH* carriers) or CRC (N=2,582; 60 *MUTYH* carriers) who had MGPT including *MUTYH* at a clinical diagnostic laboratory. Control cohorts for the BC (N=10,879; 240 *MUTYH* carriers) and CRC (N=27,514; 577 *MUTYH* carriers) comparisons included Caucasian individuals who had MGPT including *MUTYH* at the same laboratory without personal history of BC or CRC, respectively.
The frequency of all *MUTYH* mutations was compared between each of the case cohorts and the respective control cohort. Frequencies of the two most common *MUTYH* founder mutations, p.G396D and p.Y179C, were also assessed independently as well as combined. Odds ratios (OR) were obtained from logistic regression analyses after adjusting for covariates.
Results: No association was found between female BC and carrier status of any *MUTYH* mutation (OR=1.0), p.G396D alone (OR=0.9), p.Y179C alone (OR=0.9) or both founder mutations combined (OR=0.9) after controlling for personal and family history of CRC and carrier status of mutations in other genes. Similarly, no association was found between CRC and carrier status of any *MUTYH* mutation (OR=1.1), p.G396D alone (OR=1.2), p.Y179C alone (OR=0.7) or both founder mutations combined (OR=1.1) after controlling for personal and family history of female BC and carrier status of mutations in other genes.
Conclusions: In summary, these data do not support a significant association of BC or CRC risk with monoallelic *MUTYH* carrier status. To our knowledge, this is the largest cohort used to assess the association of BC risk with *MUTYH* monoallelic mutations and the first study to assess cancer association in *MUTYH* carriers identified on MGPT. Additional studies that include larger numbers of *MUTYH* mutation carriers, in addition to having larger CRC cohorts, are needed to confirm these results. Future studies should also evaluate whether *MUTYH* carriers are at increased risk for other cancers, such as gastric, liver and endometrial, given the recent literature supporting this.

	Breast Cancer			Colorectal Cancer		
	OR	**95% CI**	**P Value**	**OR**	**95% CI**	**P Value**
All mutations	1.0	0.8-1.1	0.66	1.1	0.8-1.5	0.38
Founder mutations	0.9	0.8-1.1	0.24	1.1	0.8-1.4	0.72
p.G396D	0.9	0.7-1.1	0.26	1.2	0.8-1.7	0.33
p.Y179C	0.9	0.6-1.4	0.69	0.7	0.3-1.4	0.31