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Brief Communications

# Assessment of a Polygenic Risk Score for Colorectal Cancer to Predict Risk of Lynch Syndrome Colorectal Cancer

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## Abstract

It was not known whether the polygenic risk scores (PRSs) that predict colorectal cancer could predict colorectal cancer for people with inherited pathogenic variants in DNA mismatch repair genes—people with Lynch syndrome. We tested a PRS comprising 107 established single-nucleotide polymorphisms associated with colorectal cancer in European populations for 826 European-descent carriers of pathogenic variants in DNA mismatch repair genes (293 *MLH1*, 314 *MSH2*, 126 *MSH6*, 71 *PMS2*, and 22 *EPCAM*) from the Colon Cancer Family Registry, of whom 504 had colorectal cancer. There was no evidence of an association between the PRS and colorectal cancer risk, irrespective of which DNA mismatch repair gene was mutated, or sex (all 2-sided $P > .05$). The hazard ratio per standard deviation of the PRS for colorectal cancer was 0.97 (95% confidence interval = 0.88 to 1.06; 2-sided $P = .51$). Whereas PRSs are predictive of colorectal cancer in the general population, they do not predict Lynch syndrome colorectal cancer.

Polygenic risk scores (PRSs) aggregate genetic risk variants to predict disease risk and are an emerging tool in precision medicine. For colorectal cancer, we and others have identified more than 100 single-nucleotide polymorphisms (SNPs) that, when combined as a PRS, predict colorectal cancer (1,2). A clinically important question is whether this PRS is associated with colorectal cancer risk for people who have inherited a pathogenic variant in a DNA mismatch repair (MMR) gene, that is, people with Lynch syndrome. These people have, on average, a high colorectal cancer risk, and there is evidence of unidentified genetic factors that modify their risk (3). If identified, genetic risk-modifying factors would provide an avenue for improved personalized prevention strategies for people with Lynch syndrome. A recent paper reported risks of Lynch syndrome colorectal cancer for an existing colorectal cancer PRS (4). However, the authors did not estimate these risks directly but instead simply assumed the PRS was associated with Lynch syndrome colorectal cancer, leaving the question unanswered.

We conducted an analysis of 826 people with Lynch syndrome, of whom 504 had colorectal cancer, to determine

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**Table 1.** Age at which half of the carriers developed colorectal cancer by quintile of polygenic risk score (PRS)

| Participant characteristic | No. | Age (standard error), y | | | | |
|---|---|---|---|---|---|---|
| | | Quintile 1 (n = 165) | Quintile 2 (n = 164) | Quintile 3 (n = 166) | Quintile 4 (n = 165) | Quintile 5 (n = 166) |
| PRS, range | | 0.219-0.594 | 0.595-0.804 | 0.808-1.038 | 1.045-1.380 | 1.381-3.833 |
| All genes and all carriers | 826 | 49 (1.1) | 49 (1.0) | 49 (1.6) | 48 (1.7) | 48 (1.4) |
| Gene with pathogenic variant | | | | | | |
| *MLH1* | 293 | 46 (2.2) | 45 (1.5) | 54 (3.5) | 41 (1.3) | 46 (1.9) |
| *MSH2* | 314 | 48 (1.4) | 48 (1.2) | 46 (2.4) | 49 (2.3) | 46 (3.0) |
| *MSH6* | 126 | —[a] | 56 (4.3) | 53 (4.6) | 54 (3.3) | 72 (—) |
| *PMS2* | 71 | 55 (9.7) | 57 (11) | 67(15) | 61 (7.5) | 60 (—) |
| *EPCAM* | 22 | — | 52 (3.8) | — | 48 (—) | 52 (5.1) |
| Sex | | | | | | |
| Male | 387 | 49 (1.0) | 50 (1.7) | 48 (1.2) | 46 (1.1) | 47 (1.2) |
| Female | 439 | 51 (3.0) | 48 (1.1) | 52 (2.9) | 53 (2.7) | 52 (2.4) |

[a]— = Insufficient data.

whether an existing colorectal cancer PRS is associated with Lynch syndrome colorectal cancer. Participants were from the Colon Cancer Family Registry (5), which recruited participants between 1998 and 2013, from the United States, Canada, Australia, and New Zealand: population-based colorectal cancer cases from state and regional population cancer registries; attendees with strong family histories of colorectal cancer at family cancer clinics; and relatives of these cases and attendees. Participants provided a blood sample, access to any colorectal tumors, ethnicity, and cancer and polyp history. For those whose colorectal cancer tumors were not accessed, attempts were made to verify colorectal cancer reports with cancer registrations, medical records, and relative reports. Participants were followed up every 5 years to update polyp and cancer history. Written informed consent was obtained from each participant, and research was approved by local institutional review boards.

Colorectal cancer case probands from the population-based families and colorectal cancer cases attending family cancer clinics were tested for germline variants in MMR genes. Relatives of identified carriers of pathogenic MMR germline variants were tested for their family-specific variant. Variants in *MLH1*, *MSH2*, *MSH6*, and *EPCAM* were identified by Sanger sequencing or denaturing high-performance liquid chromatography followed by confirmatory DNA sequencing (6). Variants in *PMS2* were identified using a modified protocol (7). Variants were classified for pathogenicity based on a 5-class system applied to variants cataloged within the InSiGHT database (8), with classes 4 and 5 considered pathogenic (9). Variants not yet classified by InSiGHT were considered pathogenic if predicted to result in a stop codon, frameshift, or large deletion, or if it removed a canonical splice site.

This analysis includes the 826 carriers identified as carrying a pathogenic variant in a DNA mismatch repair gene (293 *MLH1*, 314 *MSH2*, 126 *MSH6*, 71 *PMS2*, 22 *EPCAM*) of European descent and had undergone genome-wide SNP testing. SNP data for 462 carriers were from a previous testing, and genotyping, imputation, and quality control have been described (1). SNP data from the other 364 carriers were from a testing using the Infinium OncoArray-500K platform (Illumina, San Diego, USA) (10) and imputed using MiniMac v1.2.4 through the Michigan Imputation Server (11) using the European HRC r1.1 2016 reference. Filtering of the harmonized datasets for European participants was based on the first 2 principal components using the 1000 Genomes Project dataset as a reference (12). Genotypes for each of the 108 SNPs previously identified as being associated with colorectal cancer in European populations (1,2) were extracted from the harmonized set using PLINK v1.9 (13). One SNP was not included in the imputation reference panel (rs6928864), leaving 107 SNPs for this analysis (Supplementary Table 1, available online).

We analyzed data as a retrospective cohort of carriers (given the pathogenic variant is present from birth) censored at age of first polypectomy, giving 37 332 years of observation. There were 141 participants with a polypectomy and no colorectal cancer, 504 participants diagnosed with colorectal cancer with no previous polypectomy, and 75 participants with colorectal cancer diagnosed after polypectomy (included in the sensitivity analysis only; see the Supplementary Methods and Supplementary Table 2, available online).

We calculated 2 PRSs: 1) weighted sum of the number of risk alleles of each participant, using the variant's per-allele odds ratio as weights (1,2), and 2) count of the total number of risk alleles. We then tested for PRS associations with colorectal cancer risk by studying time to colorectal cancer (years of age since birth) by survival analysis and Cox regression. We allowed observations to be independent across, but nonindependent within, families by using the cluster option (14) in Stata (15) to produce robust standard errors. The PRS associations were assessed as per quintile and per standard deviation. Median observation time was 44 years (interquartile range = 36-53). All $P$ values were 2-sided, calculated by Cox regression, and significant if less than .05.

We found no difference in the age at which half of the carriers were diagnosed with colorectal cancer by quintile of PRS (see Table 1) and no association of the PRS with colorectal cancer risk (Table 2), irrespective of the MMR gene mutated, sex, or method used to calculate the PRS (all 2-sided $P \geq .05$) (see Table 2).

Lynch syndrome colorectal cancer has genotypic features involving high mutability, consistent with a different genetic etiology than non-Lynch syndrome colorectal cancer. If this genetic etiology includes polygenic factors [and there is indirect evidence that these are substantial (3)], they will not necessarily be the SNPs identified to date for colorectal cancer risk, given the vast majority of colorectal cancer is not Lynch syndrome. We did not attempt to use this study to identify SNPs associated with Lynch syndrome colorectal cancer because the number of subjects was too small for a conventional genome-wide

**Table 2.** Association between the polygenic risk score (PRS) and colorectal cancer risk

| Participant characteristic | No. of carriers | PRS using the per-allele odds ratio | | PRS using the risk allele count | |
|---|---|---|---|---|---|
| | | HR per SD (95% CI) | P[a] | HR per SD (95% CI) | P[a] |
| All genes and all carriers | 826 | 0.97 (0.88 to 1.06) | .51 | 0.99 (0.90 to 1.10) | .90 |
| Gene with pathogenic variant | | | | | |
| *MLH1* | 293 | 0.98 (0.86 to 1.12) | .79 | 0.97 (0.83 to 1.14) | .72 |
| *MSH2* | 314 | 1.02 (0.86 to 1.22) | .78 | 1.02 (0.88 to 1.17) | .83 |
| *MSH6* | 126 | 0.94 (0.76 to 1.16) | .55 | 1.02 (0.80 to 1.30) | .90 |
| *PMS2* | 71 | 0.90 (0.63 to 1.28) | .56 | 0.99 (0.76 to 1.31) | .97 |
| *EPCAM* | 22 | 1.40 (0.92 to 2.14) | .12 | 1.95 (0.94 to 4.04) | .07 |
| Sex | | | | | |
| Male | 387 | 1.01 (0.89 to 1.15) | .87 | 1.01 (0.90 to 1.14) | .81 |
| Female | 439 | 0.94 (0.83 to 1.07) | .37 | 0.98 (0.86 to 1.13) | .81 |

[a]Two-sided Cox regression, 2-sided test. CI = confidence interval; HR = hazard ratio.

associations study analysis. We are progressing a larger, collaborative Lynch syndrome–specific genome-wide association study to address this important question.

Although there is evidence that the PRS for female breast cancer might be a modifier of risk for women with pathogenic variants in *BRCA1* and *BRCA2* (16), we found no evidence that the PRS for colorectal cancer is a modifier of colorectal cancer risk because of pathogenic variants in the DNA MMR genes. Application of the PRS for colorectal cancer to Lynch syndrome is thus unwarranted.

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## Data Availability

The data from this study cannot be shared publicly due to ethical and privacy reasons. The data are available on reasonable request to the Colon Cancer Family Registry www.coloncfr.org.

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