

Colorectal Polyp Subtypes May Stem from Different Genetic Risk Loci

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Colorectal cancers generally start as colorectal polyps, which can then develop through distinct pathways into colorectal cancer. While the majority of colorectal cancers develop through the adenoma-carcinoma pathway, alternative pathways have also been identified. One of these is the serrated pathway, a phenotypically distinct pathway travelled by a subset of colorectal cancers. Genome-wide association studies have successfully identified genetic variants associated with colorectal cancer risk, but have not further explored whether these variants are also associated with particular subtypes of colorectal polyps. In a recent report in *The American Journal of Epidemiology*, Drs. Andrea Burnett-Hartman and Karen Makar and colleagues in the Public Health Sciences Division tested the association between colorectal cancer risk loci and various polyp subtypes. These associations were found to vary by subtype, suggesting that previously identified colorectal cancer risk loci play a role in early carcinogenesis for the adenoma-carcinoma pathway, rather than other pathways.

To investigate these relationships, the authors utilized data collected on 1,800 Group Health Cooperative enrollees. Tissue samples from clinical biopsies collected during colonoscopy were then classified by pathologists as one of six polyp types. Participants were categorized into case and control groups based on having either adenomas, serrated polyps, both polyp types, or no identified polyps. Participants were genotyped for thirteen single nucleotide polymorphisms (SNPs) previously identified as significantly associated with colorectal cancer. These SNPs were then analyzed, both individually and as a combined risk-allele score, for an association with each of the polyp-type groups.

Using this approach, the authors found that 5 of the 13 colorectal cancer SNPs were associated with polyps related to the adenoma-carcinoma pathway, and only one SNP was associated with the serrated pathway. Similarly, the risk score analyses showed a significant per-allele association with adenomas, but not serrated polyps. This suggests that across these 13 SNPs, increasing numbers of variant alleles raises colorectal cancer risk through the adenoma pathway but not the serrated pathway. By considering lesion severity, the authors also found that more SNPs were associated with advanced than non-advanced adenomas, suggesting that these genetic variants were likely involved in cancer promotion rather than initiation. Together, these results support the hypothesis that many of the variants previously identified for colorectal cancer risk are associated with early cancer-promoting events in the adenoma-carcinoma pathway.

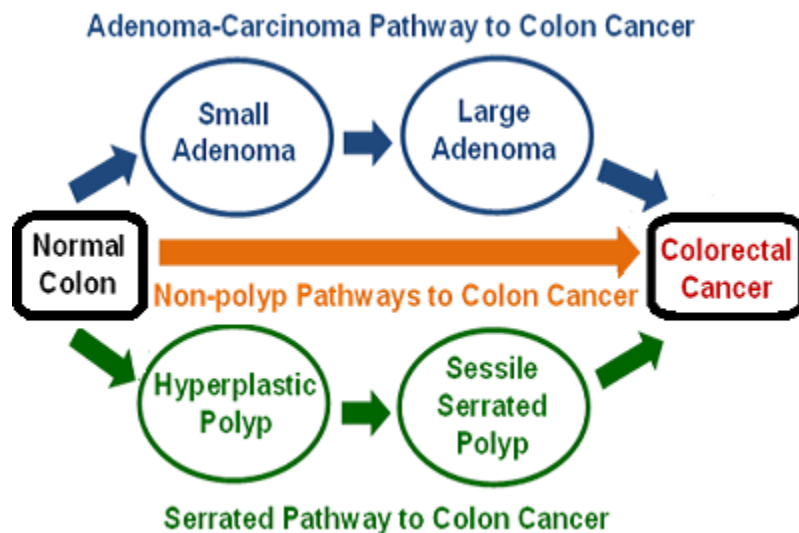
While the adenoma-carcinoma pathway accounts for roughly 75% of colorectal cancers, it is also important to characterize genetic variants that contribute to colorectal cancer risk through other pathways, such as the serrated pathway. Given the results of this study, said lead author Burnett-Hartman, "there are likely genetic variants that are important to the serrated pathway to colorectal cancer that have not yet been characterized". Identifying these additional risk variants will help paint

a more accurate picture of how genetic variants impact the various pathways through which colorectal cancer is initiated and promoted, and ultimately should better characterize genetic risk for this disease. This may be particularly important for pathways associated with later diagnosis and worse prognosis, such as the serrated pathway.

To follow-up these findings, said Burnett-Hartman, "our future research will focus on identifying genetic loci that are specifically associated with colorectal cancers that develop via the serrated pathway." For example, performing new genome-wide association studies in better-characterized colorectal cancer cases, which can then be analyzed by pathway or polyp type. Such research should be a good step towards closing the knowledge gap between colorectal cancer subtypes, especially regarding the genetic mechanisms involved in subtypes with poor outcomes.

Other PHS investigators contributing to this project were Drs. Polly Newcomb, Ulrike Peters, John Potter, and Karen Makar, as well as Mr. Michael Passarelli.

[Burnett-Hartman AN, Newcomb PA, Hutter CM, Peters U, Passarelli MN, Schwartz MR, Upton MP, Zhu LC, Potter JD, Makar KW.](#) 2014. Variation in the association between colorectal cancer susceptibility Loci and colorectal polyps by polyp type. *Am J Epidemiol.* 180(2):223-32.



(Image provided by Dr. Andrea Burnett-Hartman)

There are multiple pathways through which normal colon tissue can progress to colorectal cancer.