

Two Inflammation-Related Genes Found Associated With Rectal Cancer Risk

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JM Kocarnik

Inflammation is an important risk factor for colorectal cancer (CRC). Non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin or ibuprofen, inhibit inflammation. The use of NSAIDs has been shown to reduce colorectal cancer risk and mortality. Similarly, genetic variation in genes related to inflammation pathways also affects colorectal cancer risk and mortality. In a recent report in *Carcinogenesis*, Ms. Alexa Resler and Dr. Cornelia Ulrich and colleagues in the Public Health Sciences Division evaluated whether genetic variants in NSAID metabolism pathways may affect the chemopreventive capacity of NSAID use for colorectal cancer. Analyses revealed genetic variants in two genes that were associated with rectal cancer risk. They also found an interaction between one of these genes and NSAID use for the risk of colorectal cancer, raising the prospect of targeted NSAID use for cancer prevention.

NSAIDs act to reduce inflammation by inhibiting the activity of cyclooxygenase enzymes that control the synthesis of prostaglandins and thromboxanes (see figure). This study, said lead author Resler, "comprehensively assessed whether variation in prostaglandin synthesis and related pathways influences colorectal cancer risk." To do so, the authors identified a set of 192 single nucleotide polymorphisms (SNPs) in and around 17 genes involved in prostaglandin synthesis and related pathways. These variants were genotyped in 1600 CRC cases and 2600 sibling controls in the Colon Cancer Family Registry. The investigators analyzed these variants for an association with colorectal cancer, as well as with colon and rectal cancer individually.

While no variants were found to be associated with colon or colorectal cancer, two SNPs demonstrated a statistically significant association with rectal cancer. Interestingly, the variant alleles in these genes had effects in opposite directions. Participants with the variant allele in *ALOX12* had an almost 90% increased risk of rectal cancer (odds ratio 1.87, 95% confidence interval 1.19 – 2.95), while participants with the variant allele in *PTGER2* had an approximately 50% decreased risk of rectal cancer (odds ratio 0.49, 95% confidence interval 0.29-0.82). Said senior author Ulrich, "these results suggest that genetic variation in genes encoding enzymes that are critical in the production of leukotrienes (*ALOX12*) and prostaglandins (*PTGER2*) may affect the risk of rectal cancer."

To further characterize these relationships, the authors also assessed whether any of these genetic associations with CRC risk were modified by pre-diagnostic use of NSAIDs. After correcting for multiple comparisons, a statistically significant interaction was observed for NSAID use and another SNP in *ALOX12* on colorectal cancer risk ($p = 0.03$). Among the participants heterozygous for the variant allele, those reporting current NSAID use had an approximately 40% lower risk of CRC compared to those reporting never or former use (odds ratio 0.60, 95% confidence interval 0.42-0.80). This interaction was not statistically significant among participants homozygous for either the variant or wildtype allele.

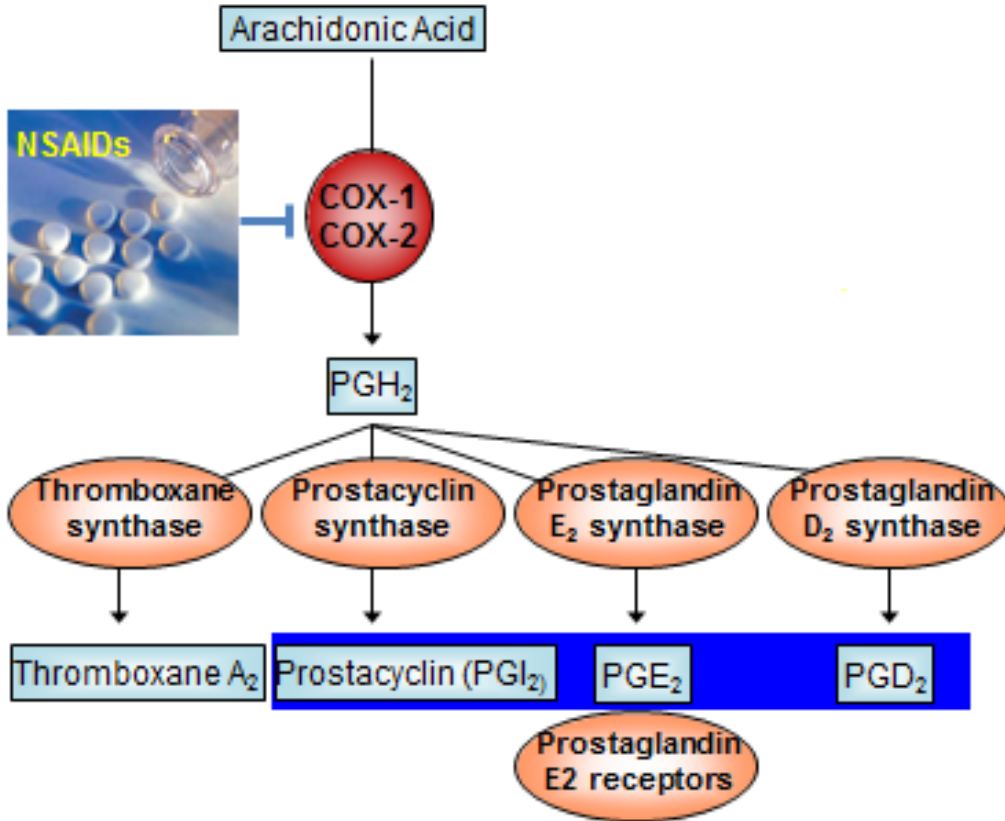
Overall, these results suggest that the expected protective association between NSAID intake and colorectal cancer risk may depend on the genetic background of an individual, raising the possibility for personalized prevention strategies. Said Ulrich, "because NSAIDs are clearly cancer preventive, yet also carry risks of side effects, the interaction between use of NSAIDs and polymorphisms in *ALOX12* is particularly exciting." Moving forward from this study, said Ulrich, "our goal is the development of genetically targeted cancer prevention strategies with NSAIDs. By identifying people who have a greater likelihood of benefitting, we can help personalize prevention."

Other PHS investigators contributing to this project were Drs. Karen Makar, John Whitton, John Potter, and Polly Newcomb, as well as Mr. Michael Passarelli and Ms. Laura Heath.

Citation:

[Resler AJ, Makar KW, Heath L, Whitton J, Potter JD, Poole EM, Habermann N, Scherer D, Duggan D, Wang H, Lindor NM, Passarelli MN, Baron JA, Newcomb PA, Le Marchand L, Ulrich CM](#). 2014.

Genetic variation in prostaglandin synthesis and related pathways, NSAID use, and colorectal cancer risk in the Colon Cancer Family Registry. *Carcinogenesis*. pii: bgu119 [Epub ahead of print].



(Image provided by Ms. Alexa Resler)

Non-steroidal anti-inflammatory drugs (NSAIDs) act to reduce inflammation by inhibiting the cyclooxygenase enzymes (COX). These COX enzymes control the conversion of arachidonic acid to prostaglandins and thromboxane, which modulate important cellular functions related to inflammation.