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The Role of Inflammatory Genes and NSAIDs in Colorectal Adenoma Recurrence

Sansbury LB, Bergen AW, Wanke KL, Yu B, Caporaso NE, Chatterjee N, Ratnasinghe L, Schatzkin A, Lehman TA, Kalidindi A, Modali R, and Lanza E. Inflammatory cytokine gene polymorphisms, nonsteroidal anti-inflammatory drug use, and risk of adenoma polyp recurrence in the Polyp Prevention Trial. *Cancer Epidemiol Biomarkers Prev* 15: 494–501, 2006.

The colorectal polyp is considered the main precursor lesion of colorectal cancer, and its removal during colonoscopy is thought to reduce colorectal cancer–related mortality. Approximately 30% to 40% of adults aged 60 years and older have colorectal polyps, and individuals with a history of a polyp are at increased risk of colorectal cancer. Identifying modifiable risk factors that affect the development and recurrence of these precancerous lesions is vital for colorectal cancer prevention strategies.

Chronic inflammation is a risk factor for many cancers, including colorectal cancer. The inflammatory response to cellular stresses, injury, and infection results from increased mucosal production of pro-inflammatory cytokines, which induce expression of cyclooxygenase-2 (COX-2), one of the key enzymes in the prostaglandin production. COX-2 is also involved in inflammation early in the carcinogenic pathway of colorectal cancer. However, the reported reduction in risk of colorectal polyps and cancer by nonsteroidal anti-inflammatory drug (NSAID) use never exceeds 50%, suggesting that non-responders to NSAIDs may attenuate their effect in colorectal cancer prevention. Thus, it is possible that individual genetic variations in inflammatory genes modify response to inflammation or to the chemopreventive effect of NSAIDs.

We therefore investigated the association between three single nucleotide polymorphisms (SNPs) in three different pro-inflammatory genes: *IL-1B* (–511 C/T, rs16944), *IL-6* (–174 G/C, rs1800795), and *IL-8* (–251 T/A, rs4073), two SNPs in the anti-inflammatory gene *IL-10* (–819 C/T, rs1800871 and –1082 G/A, rs1800896), and risk of adenoma recurrence. In addition, we investigated interactions between the inflammatory cytokine polymorphisms, NSAID use, and polyp recurrence.

Participants in this study were from the Polyp Prevention Trial (PPT), a multicenter randomized clinical trial to evaluate the effects of a high-fiber, high fruit and vegetable, low-fat diet on the recurrence of colorectal polyps. Briefly, men and women aged 35 years and older with a history of at least one histologically confirmed polyp removed were

randomized to the dietary intervention group or the control group for 4 years. A total of 1,905 (91.6%) participants completed the study and received a colonoscopy at the fourth year. Many of them (n = 1,723, 90.4%) had DNA available for genotyping, which was performed by BioServe Biotechnologies, Ltd., Laurel, MD, via a two-step PCR process and mass spectrometry. Unconditional logistic regression was used to determine odds ratios (ORs) and 95% confidence intervals (CIs) for the association between genotype and risk of any adenoma recurrence after the 4 years of the trial, as well as risk of multiple adenoma recurrence, adjusting for age, race, sex, and body mass index (BMI).

Overall, no statistically significant associations were found between any of the cytokine SNPs investigated in this study and risk of polyp recurrence. However, regular NSAID use for at least 3 years was inversely associated with risk of adenoma recurrence (OR = 0.70; 95% CI: 0.55, 0.90) and multiple polyp recurrence (OR = 0.55; 95% CI: 0.38, 0.80). Therefore, we examined the association of the cytokine polymorphisms and risk of polyp recurrence separately among NSAID and non-NSAID users. We observed a borderline significant increased risk of polyp recurrence among carriers of the *IL-10* –1082 A allele who were also NSAID users (OR = 1.55; 95% CI: 1.00, 2.43), as well as the suggestion of a 40% increased risk of multiple polyp recurrence. In contrast, we observed a statistically significant decreased risk of multiple polyp recurrence among non-NSAID users who were also carriers of the *IL-10* –1082 A allele (OR = 0.43; 95% CI: 0.24, 0.77) and a similar, but nonstatistically significant, 30% decreased risk of any polyp recurrence. There appears to be some antagonism between the *IL-10* –1082 G/A polymorphism and NSAID use in that the inverse odds ratios for NSAID use diminished among carriers of the *IL-10* –1082 A allele.

Our data mimic *IL-10*–deficient mice that develop spontaneous chronic inflammatory bowel disease, a known risk factor for colorectal cancer. *IL-10*–deficient (*IL-10*$^{-/-}$) mice have increased production of pro-inflammatory cytokines and several studies report that *IL-10*$^{-/-}$ mice treated with NSAIDs develop progressive, severe colitis much faster than *IL-10*$^{-/-}$ mice not treated with NSAIDs. On the other hand, NSAID-treated wild-type mice did not develop colitis and their colonic epithelium had no evidence of hyperplasia or ulcerations. Microscopic examination of NSAID-treated *IL-10*$^{-/-}$ mice revealed severe inflammatory infiltrates in their colonic mucosa and increased mRNA expression of inflammatory cytokines and COX-2 expression compared with NSAID-treated wild-type mice. It appears that inhibition of prostaglandin production was central to the development of NSAID-induced colitis. These results may help to explain our findings that individuals who used NSAIDs and were carriers of the *IL-10* –1082 A allele had a significantly increased risk of polyp recurrence. The *IL-10* –1082 A allele is associated with decreased production of the IL-10 anti-inflammatory cytokine and possibly, subsequently, an increased production of pro-inflammatory cytokines. These individuals might have enhanced production of cytokines if they also use NSAIDs and, in turn, could be at increased risk for adenoma recurrence.

Our results nominate the *IL-10* –1082 A allele as a genotype identifying individuals who may not benefit from the chemoprevention of colorectal cancer by NSAIDs. Future studies

investigating the role of variants of inflammatory genes that modify the chemoprotective effect of NSAIDs may help elucidate the biological mechanisms of colorectal cancer and identify individuals who will respond best to these chemopreventative agents. Such studies might also aid in the development of public health and clinical intervention programs aimed at preventing colorectal cancer.

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