Published in final edited form as:
Pharmacogenomics J. 2008 August ; 8(4): 237–247. doi:10.1038/sj.tpj.6500487.

A review of gene-drug interactions for non-steroidal anti-inflammatory drug (NSAID) use in preventing colorectal neoplasia

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to be effective chemopreventive agents for colorectal neoplasia. Polymorphisms in NSAID targets or metabolizing enzymes may affect NSAID efficacy or toxicity.

We conducted a literature review to summarize current evidence of gene-drug interactions between NSAID use and polymorphisms in *COX1*, *COX2*, *ODC*, *UGT1A6*, and *CYP2C9* on risk of colorectal neoplasia by searching the OVID and PubMed.

Of 134 relevant search results, thirteen investigated an interaction. One study reported a significant interaction between NSAID use and the *COX1* Pro17Leu polymorphism (p = 0.03) whereby the risk reduction associated with NSAID use among homozygous wild-type genotypes was not observed among NSAID users with variant alleles. Recent pharmacodynamic data support the potential for gene-drug interactions for *COX1* Pro17Leu. Statistically significant interactions have also been reported for *ODC* (315G>A), *UGT1A6* (Thr181Ala + Arg184Ser or Arg184Ser alone), and *CYP2C9* (*2/*3). No statistically significant interactions have been reported for polymorphisms in *COX2*; however an interaction with *COX2* -765G>C approached significance (p = 0.07) in one study. Among seven remaining studies, reported interactions were not statistically significant for *COX1*, *COX2*, and *ODC* gene polymorphisms. Most studies were of limited sample size. Definitions of NSAID use differed substantially between studies.

The literature on NSAID-gene interactions to date is limited. Reliable detection of gene-NSAID interactions will require greater sample sizes, consistent definitions of NSAID use, and evaluation of clinical trial subjects of chemoprevention studies.

Keywords

non-steroidal anti-inflammatory drugs; cyclooxygenase; prostaglandin H synthase; colorectal cancer; colorectal adenoma; pharmacogenetics

INTRODUCTION

The National Cancer Institute estimates that over 150,000 new cases of colorectal cancer and 52,000 deaths will be reported in the United States in 2007, making it second to lung cancer in total deaths.[1] Americans possess a one in eighteen lifetime risk of developing colorectal

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cancer.[2] Five-year relative survival rates range from 9% for distally diagnosed CRC to 90% for localized CRC. This disparity drives public health efforts to increase early detection and to slow or prevent altogether the progression of colorectal carcinogenesis.

Inflammation is a known risk factor for colorectal cancer. Several inflammatory conditions predispose to colorectal cancer, such as ulcerative colitis[3] and Crohn's disease.[4] Non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, represent a potential means of decreasing inflammation in the colonic epithelium.[5] There are two main subtypes of NSAIDs: nonselective and selective COX2 inhibitors. The COX2-selective drugs (coxibs) exhibit higher affinity for and therefore target the COX2 enzyme.[5] NSAIDs have been successful in preventing colorectal neoplasia in high-risk populations, such as subjects with a prior diagnosis of CRC or colorectal adenoma. Recently, two randomized placebo-controlled trials (RCTs) showed aspirin to significantly reduce the risk of recurrent adenomatous polyps by 19% to 35%.[6, 7] Two other RCTs showed a 33%-36% risk reduction for celecoxib and even greater reduction in the risk of advanced adenoma.[8, 9] The magnitude of risk reduction from rofecoxib versus placebo was recently shown to be comparable to that of aspirin.[10] However, rofecoxib is no longer commercially available due to concerns of cardiovascular toxicity.[11-13] Gastrointestinal and cardiovascular toxicity from aspirin/NSAID and coxibs, respectively, have spurred research to identify genetic variations which might alter the risk-benefit trade-off of these drugs in clinically meaningful ways and allow tailoring of chemoprevention.[5]

NSAIDs inhibit the cyclooxygenase (COX) activity of COX enzymes (i.e., prostaglandin H synthases), which in turn decreases prostaglandin production.[14] *COX1* is constitutively expressed in many tissues and is linked to homeostatic functions, whereas *COX2* is an inducible form involved in inflammatory and proliferative responses.[15-17] Genetic variability in downstream enzymes in the prostaglandin or lipoxygenase pathway (which competes with the COX enzymes to metabolize arachidonic acid), may also play a role in colorectal cancer, because these may affect the overall availability and balance of inflammatory mediators in the body.

Recent interest has emerged in the role of ornithine decarboxylase (ODC) and NSAIDs in colorectal cancer. NSAIDs, including celecoxib, inhibit this enzyme.[18] Whereas COX1 and COX2 mediate prostaglandin synthesis, ODC catalyzes the synthesis of polyamines, which are associated with carcinogenesis (increased cell division, up-regulation of genes involved in metastasis and tumor invasion, and down-regulation of apoptosis).[19, 20] Increased intracellular polyamine concentrations are positively associated with risk of cancer[19, 21], including sporadic colorectal cancer[22], and are negatively associated with apoptotic activity and cell death.[23] ODC is overexpressed in cancerous versus normal colon epithelium.[19, 24-27] Thus, the chemopreventive properties of NSAIDs in colorectal cancer may stem in part from their activity on ODC-mediated polyamine synthesis.[28-30]

NSAIDs are primarily metabolized by two major classes of enzymes: the cytochrome P450 2C enzymes (CYP2C) and the UDP-glucuronosyltransferases (UGTs). The major metabolizers of NSAIDs are CYP2C9[31] and UGT1A6[32], although other UGTs and CYPs may play minor roles. Both of these enzymes have common polymorphisms that are associated with less efficient drug metabolism. In *CYP2C9*, two polymorphisms, Arg144Cys (also referred to as *2) and Ile359Leu (also referred to as *3) show markedly decreased warfarin metabolism compared to wild-type.[33, 34] Similarly, there are two known variant alleles in *UGT1A6* that have been associated with decreased enzyme activity; the first is characterized by amino-acid changes at amino acids 181 and 184 (Thr181Ala + Arg184Ser) and the second by Arg184Ser alone.[35, 36] These known functional genetic polymorphisms may interact with NSAID use to affect risk of colorectal neoplasia.

Polymorphisms in *COX1*, *COX2*, and *ODC* appear to alter the risk of colorectal neoplasia.[5, 37-43] Since genetic polymorphisms and NSAID use can each modify the risk for colorectal neoplasia, pharmacogenetic studies may help to identify the population for whom NSAIDs have the most favorable risk-benefit profile for colorectal adenoma prevention. Here, we review the potential interactions between NSAIDs and genetic polymorphisms in defining risk for colorectal neoplasia and discuss future considerations for research.

RESULTS

We identified 135,360 articles about aspirin or other NSAIDs, 475,640 about polymorphisms or mutations, 223,165 that concerned the colon or rectum, and 1,610,007 that concerned neoplasia (cancer, polyp, adenom-, or neoplas-). One hundred thirty-four publications contained keywords from all four search sets. Of these, thirteen studies reported on NSAID-drug interactions where colorectal neoplasia was the clinical outcome (Table 1).

In ten of these thirteen studies, investigators reported on gene-NSAID interactions and the risk for development of colorectal adenomatous polyps; the other three reported on interactions and the risk for colorectal cancer.[42, 44, 45] All studies included age and sex as matching or adjustment variables. Other covariates included in some of the studies were smoking status, time since colonoscopy, fiber intake, alcohol consumption, BMI, and family history of colorectal cancer. The studies were conducted in primarily Caucasian populations, however two studies were conducted in African-American subjects.[41, 44] NSAID use was not consistently defined in these studies and varied by dose, duration, or frequency. Such inconsistency has the potential to lead to exposure misclassification across studies, and consequently the comparability of results. The studies ranged in size from 161 cases and 219 controls[41] to 2295 cases and 2903 controls.[45]

COX1

Four *COX1* polymorphisms (Arg8Trp, Leu15-Leu16del, Pro17Leu, and Leu237Met) have been evaluated in the literature for an interaction with NSAID exposure on the risk for colorectal neoplasia (Table 2). Although much attention has focused on the role of COX2 in NSAID pharmacodynamics, recent findings suggest a role for COX1 in colorectal carcinogenesis[46-48] and in the safety of NSAIDs, particularly coxibs.[49] Pro17Leu is a single nucleotide polymorphism that results in an amino acid change in exon 2 of the *COX1* gene.[50] In one study, NSAID use was associated with an adenoma risk reduction only among Pro17Leu wild-type NSAID users compared to wild-type nonusers (OR: 0.6; 95% CI, 0.5-0.8; p = 0.03).[50] The Pro17Leu polymorphism is located in the signal peptide of COX1 and is cleaved to form the mature protein; therefore it is unclear what functional effects this polymorphism would have. However, this polymorphism has been reported to be in complete linkage disequilibrium with a promoter polymorphism, -842A>G, which may affect binding of transcription factors.[51] The Pro17Leu variant has been associated with altered prostaglandin production[52] and coxib selectivity.[49] No statistically significant interactions have been reported for the Arg8Trp, Leu15-16del, or Leu237Met polymorphisms. Few studies have investigated potential functional effects of these *COX1* polymorphisms.[49, 51, 53] with little evidence for changes in enzyme function. However, a haplotype containing -842A>G, Arg8Trp, and Leu237Met was associated with differential aspirin response in one study.[53] The impact of *COX1* polymorphisms on peroxidase activity or peroxide regulation has not yet been studied. This is an important aspect of COX1 regulation, because peroxides are required for the initation of COX1 activity.[54] However, as is often the case with rare variant alleles, these polymorphisms may require larger studies to detect interactions.

COX2

Seventeen *COX2* polymorphisms have been tested for interaction with NSAID exposure (see Table 2 for the full list). The most commonly evaluated polymorphisms were those occurring at -765G>C and Val511Ala, the latter of which only occurs in non-Caucasian populations. One study (494 cases and 584 controls) has reported large risk reductions in colorectal adenoma for - 765 homozygous variant (CC) nonusers compared to wild-type (GG) nonusers (OR: 0.26, 95%CI: 0.07-0.89). When stratified on NSAID use, homozygous variant non-users were at decreased risk of adenoma (OR: 0.26, 95% CI: 0.07-0.89) compared to wild-type non-users, whereas there was no decrease in risk among homozygous variant NSAID users (OR: 0.82, 95% CI: 0.25-2.73). This interaction approached statistical significance (p = 0.07).[38] However, a smaller study of 337 adenoma cases and 368 controls found no evidence of interaction between this polymorphism and NSAID use.[55] The -765G>C polymorphism is relatively frequent (minor allele frequency ~17%)[38] and has been shown to suppress *COX2* promoter activity[56], although not consistently so.[57] In atherosclerosis, patients with the -765CC genotype possess significantly lower levels of C-reactive protein and interleukin-6, biomarkers of inflammatory disease.

Two studies have reported on the *COX-2* Val511Ala polymorphism (which is not found in Caucasians) and NSAID use in African-Americans. One examined this interaction in regards to colorectal cancer (240 cases and 326 controls)[44], while the other studied the interaction for distal adenoma (240 of 380 subjects were evaluated by sigmoidoscopy alone).[41] The former study noted that the significantly decreased risk of cancer among wild-type NSAID users (OR: 0.66; 95% CI, 0.45-0.95) was even greater among those carrying at least one variant allele (OR: 0.29, 95% CI, 0.08-1.06), indicating that those with a variant allele may benefit more from NSAID use. However, the interaction was statistically non-significant (p = 0.59). The latter study (161 cases, 219 controls) found significant reductions in risk among those who were either NSAID users or carried the A allele (or both) compared to those with neither exposure[41], but did not evaluate multiplicative interaction. Earlier functional analyses that showed that the Val511Ala variant did not modify the inhibitory effects of several NSAIDs, including celecoxib and indomethacin, thus an NSAID interaction with this polymorphism may be less likely.[58]

In a hospital-based case-control study conducted in Spain, subjects carrying at least one variant allele of the 9850A>G polymorphism in the *COX2* gene showed a significantly increased risk of colorectal cancer (OR: 2.49; 95% CI, 1.17-5.32).[42] The interaction with NSAID use, however, was not statistically significant (p = 0.19). This was the only study identified in the literature that reported on this polymorphism with respect to colorectal neoplasia. However, this study was fairly small (N = 292/274 controls/cases), so statistical power with respect to interactions was limited. Additionally, the use of hospital controls may bias results, because underlying comorbidities that may be associated with NSAID use can attenuate the true association between exposure (NSAID use) and outcome (cancer). This polymorphism has not been associated with functional effects, so it may be unlikely that a true association between this polymorphism and colorectal neoplasia risk exists.

ODC

Two studies have tested for interaction between the *ODC* 315G>A polymorphism and NSAID exposure and the risk for colorectal neoplasia (Table 2). This polymorphism is in a regulatory region of the gene near transcription factor binding sites and has been associated with differential RNA expression.[59] Martinez and colleagues reported that the homozygous variant (AA) genotype was associated with a significant reduction in the risk of adenoma (OR: 0.48; 95% CI, 0.24-0.99).[30] Although the NSAID interaction was not statistically significant, the risk among homozygous variant (AA) NSAID users was greatly reduced compared to wild-

type (GG) nonusers (OR: 0.10; 95% CI, 0.02-0.66); whereas a risk reduction was not observed among homozygous variant nonusers versus wild-type nonusers (OR: 0.68; 95% CI, 0.30-1.51; p-interaction = 0.13). Barry *et al.* examined specimens from an RCT and did not observe a main association with this *ODC* polymorphism on risk of adenoma, but did report a statistically significant interaction of 315G>A genotype and aspirin use on adenoma risk.[43] Aspirin users with at least one variant allele had a significant reduction in adenoma risk (RR: 0.77; 95%CI, 0.63-0.95; p-interaction = 0.04) and advanced adenoma risk (RR: 0.51; 95%CI, 0.29-0.90; p-interaction = 0.02) compared to those on placebo with at least on variant allele. No risk reduction associated with aspirin use was observed among those with the wild-type genotype. This suggests that the combination of NSAID use and *ODC* variants cumulatively reduces risk.

UGT1A6

Four studies have investigated potential interactions between the known functional polymorphisms in *UGT1A6* (Thr181Ala + Arg184Ser or Arg184Ser alone) and colorectal neoplasia risk. In a study of 441 adenoma cases and 451 controls, the risk reduction for regular aspirin users was seen only among those with at least one variant allele (OR: 0.53, 95% CI, 0.33-0.86, p-interaction not reported).[60] Similarly, in a case-control study of 313 women with adenoma and 303 control women, the risk reduction associated with regular NSAID use was stronger among women with any variant *UGT1A6* genotype compared to those with the wild-type alleles (p-interaction = 0.02).[61] Two other studies reported no interaction between *UGT1A6* genotype and NSAID use.[45, 62]

CYP2C9

Three of the studies listed above also investigated interactions between the *2 and *3 polymorphisms in *CYP2C9* and NSAID use on risk of colorectal neoplasia.[45, 60, 62] In the study by Bigler et al, the colorectal adenoma risk reduction associated with aspirin use was only seen among those with the wild-type *CYP2C9* genotype (OR: 0.50, 95% CI 0.32-0.78, p-interaction not reported). No risk reduction was seen among non-aspirin NSAID users.[60] A subsequent study found a significant interaction between the *2 and *3 genotypes and ibuprofen use, in which those with the variant alleles had a greater decrease in risk with regular ibuprofen use than those with the wild-type alleles (p-interaction = 0.02).[45] Hubner et al reported no interaction between *CYP2C9* genotypes and aspirin treatment in an RCT of aspirin for prevention of adenoma recurrence; however, the study was small, with 266 patients on aspirin and 280 on placebo.[62] The discrepancy among these three studies indicates that the interaction between *CYP2C9* polymorphisms and NSAID use requires confirmation in additional studies.

OTHER REPORTED INTERACTIONS

Although not within the scope of this review, two studies have investigated interactions between NSAID use and polymorphisms in other prostaglandin-related genes, such as *PPARγ, PPARδ, ALOX5, ALOX15,* and *PGIS*.[55, 63] Most of these have only been examined in one or two studies and results require confirmation.

DISCUSSION

We reviewed the literature for *COX1, COX2, ODC, UGT1A6,* and *CYP2C9* pharmacogenetic interactions and the risk of colorectal adenoma or cancer. To date, research has overwhelmingly focused on *COX2* polymorphisms. However, all *COX2* and NSAID pharmacogenetic interactions we identified were not statistically significant, probably in large part attributable to limited sample sizes for detecting true interactions. On the other hand, statistically significant interactions were reported for the *COX1* signal peptide polymorphism Pro17Leu, *ODC* 315G>A, *UGT1A6* Thr181Ala/Arg184Ser, and *CYP2C9* *2 and *3. The interactions for *ODC,*

UGT1A6, and *CYP2C9* have been observed in two studies, suggesting important pharmacogenetic relationships. To date, only interactions between *COX2* polymorphisms and COX2-nonselective NSAIDs have been evaluated. All polymorphisms reviewed here have yet to be tested for interactions with coxibs (e.g., celecoxib and lumiracoxib). This information will be critical to tailor cancer chemoprevention with these highly potent agents. It will also be important to evaluate these polymorphisms in conjunction with each other.

Recent randomized trials confirm the chemopreventive properties of NSAIDs in colorectal neoplasia. In one randomized trial, aspirin led to a statistically significant reduction of adenoma at three years at the 81 mg daily dose (but not at the 325 mg daily dose).[6] In another, the 325 mg dose resulted in a significant risk reduction at the 325 mg once-daily dose[7], yet the heterogeneity in response for the 325 mg dose is not well understood. Before adopting aspirin as a chemopreventive agent, understanding the sources of such variability in efficacy is warranted. The same applies to the gastrointestinal toxicity of nonselective NSAIDs, which have been estimated to cause 25% of all reported drug-related adverse events.[64] The Hypertension Optimal Treatment randomized trial demonstrated an increased risk for non-fatal major gastrointestinal bleeding among aspirin users versus placebo (RR, 1.8, $p < 0.001$)[65], specifically among female aspirin users. Although the Physicians' Health Study did not show an increased risk of gastrointestinal bleeding for aspirin users, the trial had an aspirin tolerability run-in period that would have eliminated many persons susceptible to such toxicity. Identifying genetic predictors of gastrointestinal toxicity may ultimately help to define the optimal risk-benefit for specific subpopulations.[66]

Interestingly, results from a recent cyclooxygenase inhibition study suggest that the *COX1* Pro17Leu polymorphism may play a role in the cardiotoxicity of coxibs.[49] Inhibition of COX1 by coxibs decreased in a statistically significant manner among Pro17Leu variants.[49] Decreased COX1 inhibition corresponds with increased levels of thromboxane A2 (TXA2), which is involved in platelet function. This increase would further offset an existing imbalance between COX1-derived TXA2 and COX2-derived prostacyclin resulting from the selective inhibition of COX2 by coxibs.[67, 68] If this imbalance indeed contributes to the cardiovascular risk associated with use coxibs, as has been suggested[69], our efforts to describe future tests for pharmacogenetic interactions should consider cardiovascular risk as an outcome of interest, in addition to that of colorectal neoplasia.

Some have questioned altogether whether coxibs should continue to be evaluated for their potential as colorectal chemopreventive agents[70], due to the known cardiovascular risks associated with this class of drugs[71-74] that are not observed with other NSAIDs such as aspirin.[66] The value of coxibs for chemoprevention will therefore lie in our ability to define the population of individuals at most likely to benefit and to be less likely to experience drug-related serious adverse events. When deciding on how to minimize their risk of colorectal cancer, certain populations at increased risk of cancer, such as those with familial adenomatous polyposis, may place greater value on the cancer-preventive properties of coxibs than on their potential for cardiovascular adverse events.[75] We ought to consider the efficacy and adverse effects of all available NSAIDs to tailor chemoprevention based on genetic and other factors in favor of the greatest benefit:risk ratio.

In summary, inflammation is an established risk factor for colorectal cancer and polymorphisms in genes regulating inflammatory processes appear to alter the risk for neoplasia and the efficacy of NSAIDs in colorectal cancer chemoprevention. Studies investigating potential interactions between NSAID use and genetic polymorphisms in inflammation have been of limited power due to inadequate sample size; studies with fewer than 400 cases and 400 controls are most likely underpowered for detecting most gene-NSAID interactions. Our understanding of pharmacogenetic interactions between anti-inflammatory

drug use and genetic polymorphisms and these health outcomes may pave the road to chemoprevention of colorectal cancer by allowing us to optimize the risk-benefit balance associated with NSAIDs.

METHODS

Search terms were used to identify publications that assessed interactions between NSAID use and polymorphisms in NSAID-related genes (i.e. *CYP2C9, UGT1A6*, and *prostaglandin synthase*) on the risk of colorectal neoplasia from the Ovid MEDLINE® database.[76] We queried the titles, abstracts, and keywords of indexed and in-process publications through April 26, 2007. We searched for articles containing main effects of NSAID/aspirin drug exposure and gene polymorphisms and colorectal neoplasia using the following four sets of search terms: (1) NSAID, antiinflammatory, anti-inflammatory, nonsteroidal, non-steroidal, aspirin, or *acetylsalicylic*, and (2) *polymorphism, variant*, or *mutation*, and (3) *cancer, adenom-, polyp*, or *neoplas-*, and (4) *colon, rectum, rectal, colorectal*, or *colonic*. We considered relevant articles to be any that contained at least one term from each set of keywords and reviewed content for analyses of potential gene-NSAID interactions.

We abstracted information on the study design (including sample size, covariates, endpoint measures, and inclusion criteria), the risk estimates for the gene and drug main associations, and the results from interaction tests.

Acknowledgements

Work was supported by grants from the National Institutes of Health R01 CA114467; R03 CA123577; R25 CA094880, and R25 CA092408-06 We would like to thank Rachel Galbraith for her technical assistance with the manuscript.

Abbreviations used

CI, confidence interval; COX, cyclooxygenase; NSAIDs, non-steroidal anti-inflammatory drugs; ODC, ornithine decarboxylase; OR, odds ratio; PTGS1, prostaglandin H synthase1; PTGS2, prostaglandin H synthase 2; hzv, heterozygous variant.

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Table 1

Characteristics of studies evaluating gene-NSAID interactions*

Study	Genes	Study design	# Cases/controls	NSAID use	Study region	Colorectal study endpoint	Population description	Covariates
Lin 2002[41]	COX2	Case-control	161/219	Not defined	California/North Carolina	Adenomatous polyp; Cancer	African-American; 30-74 years old; spoke English	Matched: age, sex, sigmoidoscopy date, center
Bigler 2001[57]	CYP2C9 UGT1A6	Case-controls	441/488	ASA/ NSAID users: >once daily for >1 year	Minnesota	Adenomatous polyp	30-74 years old	Adjusted: age, sex, smoking, hormone replacement therapy
Martinez 2003[30]	ODC	Case-control	341/347	ASA use collected, not defined	Arizona	Adenomatous polyp	40-80 years old	Adjusted: age, sex, # colonoscopies after baseline
Cox 2004[42]	COX2	Case-control	292/274	Regular use for at least 6 consecutive months	Spain	Cancer	Presented only as ORs	Matched: age, sex
Ulrich 2004[37]	COX1	Case-control	715/621	Regular ASA/ NSAID use: > once daily	Minnesota	Adenomatous, hyperplastic polyp	Caucasian; English speaking; 30-74 years old	Adjusted: age, sex
Ali 2005[73]	COX2	Case-control	726/729	Use of Aspirin, Ibuprofen, none or both (not clearly defined)	USA	Advanced adenomatous polyp	Caucasian; 55-74 years old	Matched: age, sex Adjusted: age, sex, smoking, NSAID
Chan 2005[58]	UGT1A6	case-control	530/532	ASA users: twice weekly	USA	Adenomatous polyp	Not reported	Adjusted: age, smoking hx, BMI, physical activity, family hx of CRC, meat intake, alcohol intake, multivitamin use, folate intake, calcium intake
Ulrich 2005[38]	COX2	Case-control	690/584	Regular ASA/ NSAID users: > once daily	Minnesota	Adenomatous, hyperplastic polyp	Caucasian; English-speaking; 30-70 years old.	Adjusted: age, sex, BMI, calories, alcohol, fiber, hormone use, & smoking

Table 2

Interactions of NSAID use reported in the literature for COX1, COX2, or ODC and risk of colorectal neoplasia

Mutation	Primary Outcome	Main effect OR [95%CI]	OR comparison	Interactions	Interaction Comparison	1st Author Yr
COX1						
Leu15-Leu16del	Adenomatous polyps	3.6 [1.2-11.2]	het vs. wt	p = 0.12	Leu15-16del potentially associated with stronger risk of adenoma among nonusers of ASA/NSAID.	Ulrich 2004[37]
	Hyperplastic polyps	2.1 [0.5-9.1]	het vs. wt			Ulrich 2004[37]
Leu237Met	Adenomatous polyps	0.8 [0.5-1.4]	het vs. wt	p = 0.22	No significant interaction, but ASA/NSAID use ↓ risk for Leu237 wt (OR: 0.6; 95% CI 0.5-0.9) but not for Leu237 het/hzv.	Ulrich 2004[37]
	Adenomatous polyps	0.86 [0.28-2.67]	het/hzv vs. wt	No significant interaction.		Siezen 2006[53]
	Hyperplastic polyps	1.0 [0.5-2.0]	het vs. wt			Ulrich 2004[37]
Pro17Leu	Adenomatous polyps	0.9 [0.6-1.2]	het/hzv vs. wt	**p = 0.03**	ASA/NSAID use ↓ risk for P17L wt (OR: 0.6; 95% CI 0.5-0.8) but not P17L het/hzv.	Ulrich 2004[37]
	Hyperplastic polyps	0.7 [0.4-1.1]	het/hzv vs. wt			Ulrich 2004[37]
Arg8Trp	Adenomatous polyps	1.1 [0.8-1.6]	het/hzv vs. wt	p = 0.31	No significant Arg8Trp*NSAID interaction.	Ulrich 2004[37]
	Hyperplastic polyps	1.2 [0.8-1.9]	het/hzv vs. wt			Ulrich 2004[37]
Trp8Arg	Adenomatous polyps	0.90 [0.49-1.65]	het/hzv vs. wt	No significant interaction.		Siezen 2006[53]
COX2						
-1329A>G	Adenomatous polyps	1.20 [0.78-1.84] 0.95 [0.34-2.65]	het vs. wt hzv vs. wt	No significant interaction.		Siezen 2006[53]
T5229G	Advanced adenomatous polyps	0.94 [0.74-1.20] 0.73 [0.42-1.27]	het vs. wt hzv vs. wt			Ali 2005[73]
-663 GTdel	Advanced adenomatous polyps	0.65 [0.40-1.04]	het del vs. wt		Interaction studied in haplotype analysis only.	Ali 2005[73]
-765G>C	Adenomatous polyps	1.12 [0.70-1.78]	het/hzv vs. wt	No significant interaction.		Siezen 2006[53]
	Adenomatous polyps (n=494)	1.00 [0.74,1.35]	het vs. wt	0.66 [0.48-0.92] 1.02 [0.69-1.51] 0.64 [0.40-1.02] 0.26 [0.07-0.89] 0.82 [0.25-2.73] p = 0.07	Wt users vs. wt nonusers Het nonusers vs wt nonusers Het users vs wt nonusers Hzv nonusers vs wt nonusers Hzv users vs wt nonusers Hzv genotype Marginally nonsignificant interaction for NSAID use & genotype (P = 0.07, het/hzv vs wt). ↓ risk for hzv non	Ulrich 2005[38]
	Adenomatous polyps (n=494)	0.53 [0.22-1.28]	hzv vs. wt			Ulrich 2005[38]
	Hyperplastic polyps(n=186)	0.97 [0.65-1.46]	het vs. wt			Ulrich 2005[38]
	Hyperplastic polyps(n=186)	0.24 [0.05-1.11]	hzv vs. wt			Ulrich 2005[38]
-798A>G	Advanced adenomatous polyps	1.02 [0.81-1.27] 0.80 [0.43-1.50]	het vs. wt hzv vs. wt			Ali 2005[73]
T8494C	Advanced adenomatous polyps	1.17 [0.94-1.46] 1.14 [0.82-1.59]	het vs. wt hzv vs. wt			Ali 2005[73]

Mutation	Primary Outcome	Main effect OR [95%CI]	OR comparison	Interactions	Interaction Comparison	1st Author Yr
G10335A	Cancer	2.17 [0.99-4.78]	het/hzv vs. wt			Cox 2004[42]
C1629G	Cancer	1.59 [0.56-4.52]	het vs. wt hzv vs. wt			Cox 2004[42]
T2242C	Adenomatous polyps	1.30 [0.86-1.98] 1.15 [0.55-2.41]	het vs. wt hzv vs. wt	Non significant interaction.		Siezen 2006[53]
G3050C	Cancer	1.30 [0.90-1.87] 1.50 [0.63-3.57]	het vs. wt hzv vs. wt			Cox 2004[42]
A401G	Cancer	0.92 [0.62-1.38] 0.78 [0.33-2.05]	het vs. wt hzv vs. wt			Cox 2004[42]
5209T>G	Cancer	1.05 [0.73-1.52] 0.99 [0.42-2.33]	het vs. wt hzv vs. wt			Cox 2004[42]
T8473C	Cancer	1.01 [0.71-1.45] 1.05 [0.58-1.91]	het vs. wt hzv vs. wt			Cox 2004[42]
G926C	Cancer	0.92 [0.61-1.39] 1.13 [0.46-2.80]	het vs. wt hzv vs. wt			Cox 2004[42]
A9850G	Cancer	2.49 [1.17-5.32]	het/hzv vs. wt	NSAID*9850A>G nonsignificant (p-value = 0.19). ↓ risk for wt homozygous (AA=0.55 [0.36-0.84]). Het/hzv users ↑ risk vs. nonusers (AG/GG=1.08, 95% CI 0.17-6.77).	NSAID*9850A>G wt homozygous het/hzv	Cox 2004[42]
Val102Val (G>C)	Adenomatous polyps	0.65 [0.42-1.01]	het/hzv vs. wt	No significant interaction.		Siezen 2006[53]
Val511Ala	Cancer	0.67 [0.28-1.56]	het/hzv vs. wt			Lin 2002[41]
	Cancer	1.19 [0.39-3.61]	het/hzv vs. wt excluding NSAID users			Lin 2002[41]
	Cancer	0.62 [0.33-1.16]	het/hzv vs. wt	p = 0.59	Interaction no statistically significant. Significant ↓ risk among wt users (0.66, 0.45-0.95) was nonsignificant among het/hzv users.	Sansbury 2006[45]
	Adenomatous polyps	0.56 [0.25-1.27]	het/hzv vs. wt			Lin 2002[41]
	Adenomatous polyps	0.29 [0.08-1.08]	het/hzv vs. wt excluding NSAID users			Lin 2002[41]
ODC						
G315A	Adenomatous polyps	1.03 [0.89-1.20] 0.98 [0.73-1.32] 1.02 [0.88-1.17]	het vs. wt hzv vs. wt het/hzv vs. wt	**p = 0.04**	Significant interaction: ASA use ↓ adenoma risk for ODC 315G>A het/hzv but not for wt.	Barry 2006[43]
	Advanced lesions	0.90 [0.61-1.34] 0.70 [0.29-1.69] 0.89 [0.61-1.30]	het vs. wt hzv vs. wt het/hzv vs. wt	**p = 0.02**	Significant interaction: ASA use ↓ advanced lesion risk for ODC 315G>A het/hzv but not for wt.	Barry 2006[43]
	Adenomatous polyps	0.96 [0.68-1.34] 0.48 [0.24-0.99]	het vs wt hzv vs wt	p = 0.13	No interaction between ODC*ASA use and adenoma risk.	Martinez 2003[30]
	Adenomatous polyps	1.05 [0.70-1.58] 0.68 [0.30-1.51]	het nonuser vs wt nonuser hzv nonuser vs wt nonuser			Martinez 2003[30]

Mutation	Primary Outcome	Main effect OR [95%CI]	OR comparison	Interactions	Interaction Comparison	1st Author Yr
	Adenomatous polyps	0.83 [0.51-1.34] 0.64 [0.37-1.09] 0.10 [0.02-0.66]	wt user vs wt nonuser het user vs wt nonuser hzv user vs wt nonuser			Martinez 2003[30]
UGT1A6						
Thr181Ala + Arg184Ser	Adenomatous polyps	0.97 [0.74-1.26]	het/hzv vs. wt		Risk reduction with ASA use stronger among those with any variant allele.	Bigler 2001[57]
	Adenomatous polyps	0.74 [0.39-1.41] 0.41 [0.24-0.71]	wt user (>7 pills/ week) vs.wt nonuser variant allele user (>7 pills/week) vs. variant allele nonuser	p = 0.02	Risk reduction with ASA use stronger among those with variant allele.	Chan 2005[58]
	Adenomatous polyp recurrence	0.68 [0.52-0.89]	het/hzv vs. wt	p = 0.70	No interaction between ASA use and *UGT1A6* variant alleles for polyp recurrence	Hubner 2006[59]
	Cancer	1.08 [0.94-1.24] 0.94 [0.76-1.15]	het/hzv vs. wt (colon cancer) het/hzv vs. wt (rectal cancer)	p = 0.39 (ibuprofen) p = 0.40 (ASA)	No interaction between *UGT1A6**ASA/ibuprofen use and adenoma risk.	Samowitz 2006[46]
CYP2C9						
	Adenomatous polyps	1.10 [0.83-1.46]	het hzv vs. wt		Risk reduction with ASA use stronger among those wt.	Bigler 2001[57]
	Adenomatous polyp recurrence	1.09 [0.82-1.44]	het hzv vs. wt	p = 0.98	No interaction between ASA use and *CYP2C9* variant alleles for polyp recurrence	Hubner 2006[59]
	Cancer	1.04 [0.90-1.21] 0.93 [0.76-1.14]	het hzv vs. wt (colon cancer) het hzv vs. wt (rectal cancer)	p = 0.41 (ibuprofen) **p = 0.02** (ASA)	Risk reduction with ASA use stronger among those with variant allele; no interaction with ibuprofen use.	Samowitz 2006[46]