

Ornithine Decarboxylase G316A Genotype Is Prognostic for Colorectal Adenoma Recurrence and Predicts Efficacy of Aspirin Chemoprevention

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Abstract Purpose: The chemopreventive activity of aspirin in colorectal neoplasia may be explained in part by its effect on polyamine metabolism. The ornithine decarboxylase (ODC) G316A polymorphism affects polyamine metabolism through altered expression of ODC. We investigated the influence of *ODC* G316A on the chemopreventive activity of aspirin in colorectal adenoma (CRA) recurrence.

Experimental Design: We genotyped *ODC* G316A in 546 individuals in the United Kingdom Colorectal Adenoma Prevention trial of aspirin for CRA recurrence prevention and pooled our findings with data from two other randomized intervention trials.

Results: The United Kingdom Colorectal Adenoma Prevention participants with homozygous *ODC* 316AA genotype were at reduced CRA recurrence risk [relative risk (RR), 0.43; 95% confidence interval (95% CI), 0.16-1.15], particularly if also exposed to aspirin (RR, 0.24; 95% CI, 0.03-1.71). In the pooled analysis of 2,207 individuals, those with homozygous *ODC* 316AA genotype were at significantly reduced CRA recurrence risk (RR, 0.68; 95% CI, 0.47-0.99). Following stratification by genotype and aspirin exposure, individuals with homozygous wild-type or heterozygous genotypes derived modest benefit from aspirin (RR, 0.85; 95% CI, 0.72-1.01), whereas in those with both *ODC* 316AA genotype and aspirin exposure recurrence risk was halved (RR, 0.52; 95% CI, 0.29-0.91).

Conclusion: The *ODC* G316A genotype is prognostic for CRA recurrence and predictive of an enhanced response to aspirin in preventing recurrence. This variant has the potential to be a clinically useful genetic marker to identify individuals likely to derive the greatest benefit from aspirin chemoprevention.

Aspirin and nonsteroidal anti-inflammatory drugs (NSAID) have established chemopreventive activity against the development and recurrence of colorectal neoplasia (1–4). Their use in primary and secondary prevention of colorectal neoplasia is not currently recommended as not all individuals derive benefit and some experience side effects (5, 6). Identification of genetic factors predictive of aspirin response could allow targeted prevention to individuals predisposed to gain differential benefit, thus altering the balance between benefit and risk.

Aspirin and NSAIDs influence polyamine levels by induction of polyamine catabolism, and this mechanism may in part account for their chemopreventive effects on colorectal neoplasia (7). Polyamines are organic cations formed by decarboxylation of the amino acids ornithine or arginine by urea cycle enzymes, which are widely expressed in all tissues (8). Polyamines affect many processes in carcinogenesis, and inhibition of polyamine synthesis is associated with reduced cell proliferation, increased apoptosis, and suppression of angiogenesis (7, 9). Ornithine decarboxylase (ODC) is the first and rate-limiting enzyme in the polyamine synthesis pathway (8). Polyamine levels and ODC activity are increased in many human epithelial tumors, including colon cancer, whereas pharmacologic inhibition of ODC suppresses cancer development in animal models (9–11). The *ODC* gene is a target for the transcription factor MYC, and loss of adenomatous polyposis coli (APC) function that occurs early in colorectal tumorigenesis results in overexpression of the *MYC* oncogene and, hence, increased synthesis of ODC (Fig. 1; ref. 12).

Expression of the ODC enzyme is altered by the functional *ODC* G316A polymorphism (13, 14). This variant lies between two promoter region transcription factor binding sites, and the minor allele confers reduced ODC enzyme expression (14). Aspirin and *ODC* G316A genotype act independently at different stages of polyamine metabolism to reduce tissue

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Note: The list of members of the UKCAP Consortium is available on request.

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polyamine levels; thus, genotype for this variant may influence the chemopreventive activity of aspirin in colorectal neoplasia.

A prognostic influence of the *ODC G316A* polymorphism in colorectal adenoma (CRA) recurrence, and a predictive influence of the same variant in determining response to aspirin in preventing CRA recurrence, has been suggested; however, consensus on which genotypes confer reduced recurrence risk has not been reached (14, 15). By genotyping 546 individuals who participated in a randomized intervention trial of aspirin for the prevention of CRA recurrence, and combining our findings with data from two previous studies, we show that the *ODC G316A* polymorphism acts in a recessive manner influencing both CRA recurrence and response to aspirin chemoprevention.

Materials and Methods

Study participants. The United Kingdom Colorectal Adenoma Prevention (UKCAP) trial is a recently completed multicenter, double-blind, randomized, controlled trial of aspirin and folate for the prevention of CRA recurrence (16). Eligible patients had one or more histologically confirmed CRA removed at full colonoscopy in the 6 mo before enrollment and were not taking regular aspirin, nonaspirin NSAID, or prescribed folate supplements. Patients were randomized to aspirin alone (300 mg daily), folate alone (500 µg daily), both aspirin and folate, or double placebo. The primary endpoint was CRA recurrence defined as histologically confirmed recurrence of CRA or colorectal cancer (CRC) occurrence.

Recurrence was ascertained at follow-up colonoscopy scheduled for 3 y after entry colonoscopy or done earlier if symptoms dictated. If follow-up colonoscopy was done before the 3-y time point and CRA or CRC was found, then the patient left the trial, and if no adenoma was found, then the patient continued on trial medication and underwent further colonoscopy at the 3-y time point. Suspected recurrences found at follow-up colonoscopy were reviewed by the same histopathology department as the original trial entry specimen. Histopathology was done at local hospitals without central review.

Between 1997 and 2001, 945 patients were recruited, of which 942 were eligible and were randomized. Information on results of follow-up colonoscopy (at 3 y or earlier) was available for 853 patients. Blood samples for extraction of germ-line DNA were collected from 546 patients. Not all patients from the original trial could be included in this molecular subprotocol as some could not be contacted and others did not consent to DNA analysis. All patients included in the genotyping analyses were of Caucasian ethnicity.

Information on lifestyle factors, including ethnicity and detailed family history data, was obtained from all study participants by dedicated interviewers during face-to-face interviews. Compliance with trial medication was assessed at 4-monthly intervals by research nurses during either telephone interviews or home visits. Patients were asked directly about compliance and potential side effects, and trial tablets were counted. At initial recruitment and follow-up visits, patients were asked to use acetaminophen for pain relief where necessary and to avoid the use of NSAIDs. In terms of compliance, 74% of patients continued in the aspirin arm (aspirin or aspirin-placebo) until follow-up colonoscopy, and in 94% of these, there was ≥85% compliance with prescribed tablets. The incidence of adverse events, including gastrointestinal bleeding, stroke, and dyspeptic symptoms, was not significantly different in the aspirin- and nonaspirin-containing arms of the trial.

Informed consent for the study was obtained from all participants and the study was carried out with ethical review board approval in accordance with the tenets of the Declaration of Helsinki.

Genotyping. Constitutional DNA was extracted from EDTA venous blood samples using a standard salt extraction procedure and quantified by PicoGreen (Invitrogen). *ODC G316A* genotypes were generated using Taqman technology implemented on an ABI 7900HT sequence detection system (Applied Biosystems). The genotyping assay was validated using control samples of known homozygote wild-type, heterozygote, and homozygote variant genotype generated by direct sequencing. A random 10% of samples were repeated with complete concordance. Details of PCR primer sequences and reaction conditions are available on request.

Details of studies included in meta-analysis. The relationship between *ODC G316A* genotype, aspirin use, and CRA recurrence has been investigated in two previous studies (Table 1; refs. 14, 15). Martinez et al. (2003) reported data from a randomized trial of wheat bran fiber intervention for CRA recurrence prevention in which information on aspirin use was prospectively collected by self-administered questionnaire at baseline (17). *ODC G316A* was genotyped in 688 individuals, 209 (30%) of whom reported aspirin use. Barry et al. (2006) reported *ODC G316A* genotype from 973 participants in the Aspirin/Polyp Prevention Study (2) who were randomly assigned to placebo or aspirin treatment (81 or 325 mg daily). In both studies, the primary end point was CRA recurrence defined as recurrence of one or more CRA or CRC occurrence.

Statistical analysis. Genotype frequencies were tested for departure from Hardy-Weinberg equilibrium using the χ^2 test. The relationship between genotype and risk of recurrence was assessed by means of relative risks (RR) and 95% confidence intervals (95% CI) calculated using Poisson regression with robust error variance, adjusting for sex and interval between entry and follow-up colonoscopy because these two variables were found to significantly influence recurrence risk. The

Table 1. Details of studies included in the meta-analysis

Study	Trial	Country	Ethnicity*	Total trial participants/genotyped subjects	Proportion exposed to aspirin	Aspirin dose	<i>ODC 316A</i> allele frequency	<i>ODC 316AA</i> genotype frequency
Martinez et al. (14)	Wheat bran fiber (17)	United States	Predominantly Caucasian	1,304/688	30%	Variable †	0.25	6%
Barry et al. (15)	Aspirin/Folate Polyp Prevention Study (2)	United States	Predominantly Caucasian	1,084/973	66%	81 or 325 mg (50% each)	0.27	7%
This study	UKCAP (16)	United Kingdom	Caucasian	853/546	49%	325 mg	0.24	5%

*Ethnicity of genotyped individuals.

†Participants were categorized as aspirin exposed if they had consumed aspirin in the month before completing a self-administered questionnaire.

likelihood ratio test was used to explore interactions between genotype and aspirin treatment with respect to recurrence risk by comparing models with and without a multiplicative term for the two variables.

The relationship between recurrence and ODC G316A genotype in this and two previously published studies was formerly evaluated by pooling data using standard meta-analytic techniques. Fixed-effects summary RRs and 95% CIs were calculated by averaging the natural logarithms of the RRs from individual studies, weighted by the inverses of their variances (18). For the purposes of these analyses, crude RRs and 95% CIs were calculated from published raw data. Cochran's *Q* statistic was used to formally test for heterogeneity, and the percentage variability of the pooled RR attributable to heterogeneity between studies was quantified using the *I*² statistic (19).

Statistical analyses were undertaken using STATA version 7.0 (Stata Corp.). Power calculations were undertaken using the method published by Ury and Fleiss (20), as implemented in the statistical program POWER version 1.30 (Epicenter Software). All statistical tests were two sided.

Results

There were no significant differences in age, sex, intervention group, interval between entry and follow-up colonoscopy, and outcomes between the total UKCAP trial population and patients included in the genotyping analysis (Table 2). Of the 546 genotyped patients, 130 (23.8%) had ≥ 1 CRA and 7 (1.3%) had CRC detected at follow-up colonoscopy. Seventy patients (12.8%) had advanced colorectal neoplasia, defined as CRAs with villous or tubulovillous features, size ≥ 1 cm, severe dysplasia, or invasive carcinoma. In the main trial, a reduced CRA recurrence risk was observed in patients who received aspirin (RR, 0.81; 95% CI, 0.65-1.02; ref. 16), and in the genotyped subgroup, a smaller recurrence risk reduction was observed (RR, 0.92; 95% CI, 0.70-1.22). Folate did not influence recurrence risk in either the main trial or the genotyped subgroup.

Genotype frequencies for the ODC G316A polymorphism were consistent with those previously reported in Caucasian populations, with 37.9% and 5.3% of individuals being heterozygous and homozygous, respectively, for the rarer A allele (13). Genotype frequencies were in Hardy-Weinberg equilibrium ($P = 0.46$). Compared with homozygous wild-type individuals, those with homozygous ODC 316AA genotype showed a trend toward a reduced risk of recurrence (RR, 0.43; 95% CI, 0.16-1.15), whereas heterozygous genotype had little influence on recurrence risk (Table 3). When only advanced lesion recurrence was considered, a similar pattern was observed with a trend toward reduced recurrence risk in ODC 316AA homozygotes.

Following stratification by both genotype and aspirin treatment, the protective effect of the homozygous ODC 316AA genotype seemed to be enhanced by concomitant aspirin treatment. When compared with homozygous wild-type individuals who received placebo, those with homozygous variant genotype who received aspirin had a markedly reduced recurrence risk (RR, 0.24; 95% CI, 0.03-1.71). The interaction between genotype and aspirin treatment, however, was not significant ($P_{\text{int}} = 0.55$).

In the meta-analysis, the effect of ODC G316A genotype and aspirin exposure was examined in a combined cohort of 2,207 individuals in which a recurrence was observed in 912. Because the results of our study, along with a previous CRA recurrence study and functional studies (14), suggest a recessive mode of

Table 2. Comparison of the total UKCAP trial population and patients genotyped in this study

Variable	UKCAP trial population	Genotyped patients
<i>n</i>	853	546
Age*		
Mean (y)	57.5	57.3
SD	9.3	9.3
Sex, <i>n</i> (%)		
Male	477 (56)	289 (53)
Female	376 (44)	256 (47)
Intervention, <i>n</i> (%)		
Folate alone	215 (25.2)	144 (26.4)
Aspirin alone	217 (25.4)	131 (24.0)
Folate and aspirin	217 (25.4)	135 (24.7)
Double placebo	204 (23.9)	136 (24.9)
Colonoscopy interval †		
Mean (mo)	40.3	40.7
SD (mo)	12.2	11.7
Range (mo)	2-79	6-74
Outcome, <i>n</i> (%) ‡		
Adenoma	207 (24.2)	130 (23.8)
Carcinoma	11 (1.3)	7 (1.3)
Advanced neoplasia	104 (12.2)	70 (12.8)

*Age at entry colonoscopy.

†Interval between entry and follow-up colonoscopy (mean, SD, and range).

‡Follow-up colonoscopy outcome definitions were as follows: "adenoma," histologically confirmed colorectal adenoma; "carcinoma," histologically confirmed colorectal carcinoma; and "advanced neoplasia," colorectal adenoma ≥ 1 cm diameter, villous or tubulovillous histology, severe dysplasia, or colorectal carcinoma.

action, we compared individuals with homozygous ODC 316AA genotype with those of heterozygous and homozygous ODC 316GG genotypes combined. In the pooled analysis, individuals with homozygous ODC 315AA genotype had a significantly reduced recurrence risk (RR, 0.68; 95% CI, 0.47-0.99; $P = 0.04$), with no significant heterogeneity between studies ($Q = 1.8$; $P = 0.4$; $I^2 = 0\%$). Figure 2 illustrates the results of the pooled analysis following stratification by both genotype and aspirin exposure. In homozygous ODC 316GG and heterozygous individuals, aspirin exposure was associated with a modest reduction in recurrence risk (RR, 0.85; 95% CI, 0.72-1.01). Aspirin exposure in ODC 316AA genotype individuals, however, resulted in a 48% reduction in recurrence risk (RR, 0.52; 95% CI, 0.29-0.91; $P = 0.02$), with no significant heterogeneity between studies ($Q = 2.3$; $P = 0.3$; $I^2 = 14\%$).

Discussion

The results of our analysis of participants in the UKCAP trial provide evidence that the ODC G316A polymorphism influences CRA recurrence; however, due to the low frequency of the ODC 316A allele, the number of individuals with ODC 316AA genotype was small, making estimates of genotype-recurrence associations imprecise. To address this issue, we did a meta-analysis including data from our own and two previously published randomized trials of CRA recurrence. Whereas the analysis of UKCAP participants had 80% and 20% power to detect an effect of genotype in dominant and recessive models, respectively, assuming a variant allele

Table 3. Association of *ODC* G316A genotype and adenoma recurrence in all subjects and following stratification by aspirin treatment

ODC genotype	All subjects		Aspirin treatment			
	Recurrence/ total (%)	RR (95% CI)*	Recurrence/ total (%)	RR (95% CI)*	Recurrence/ total (%)	RR (95% CI)*
All adenomas						
GG	82/310 (26.5)	1.00 (reference)	44/156 (28.2)	1.00 (reference)	38/154 (24.7)	0.88 (0.62-1.26)
GA	52/207 (25.1)	0.92 (0.70-1.21)	28/111 (25.2)	0.85 (0.56-1.23)	24/96 (25.0)	0.88 (0.58-1.32)
AA	3/29 (10.3)	0.43 (0.16-1.15)	2/13 (15.4)	0.56 (0.20-1.60)	1/16 (6.25)	0.24 (0.03-1.71)
Advanced lesions †						
GG	37/310 (11.9)	1.00 (reference)	22/156 (14.1)	1.00 (reference)	15/154 (9.7)	0.69 (0.33-1.32)
GA	31/207 (15.0)	1.18 (0.78-1.81)	18/111 (19.4)	1.02 (0.60-1.73)	13/96 (13.5)	0.93 (0.50-1.72)
AA	2/29 (6.9)	0.62 (0.15-2.56)	1/13 (7.7)	0.55 (0.07-4.17)	1/16 (6.3)	0.49 (0.06-4.14)

*RR and 95% CIs adjusted for sex and interval between entry and follow-up colonoscopy.

† Advanced lesions were defined as colorectal adenomas with villous or tubulovillous features, size ≥ 1 cm, severe dysplasia, or colorectal carcinoma.

frequency of 0.24 and a RR of 0.5 associated with the variant allele, the meta-analysis had over 90% and 80% power, respectively. Consistent with this increased power, the influences of *ODC* G316A genotype in the meta-analysis were

statistically significant and indicate that homozygous carriers of the *ODC* 316A allele not only are at reduced risk of CRA recurrence but also show an enhanced response to aspirin in preventing recurrence.

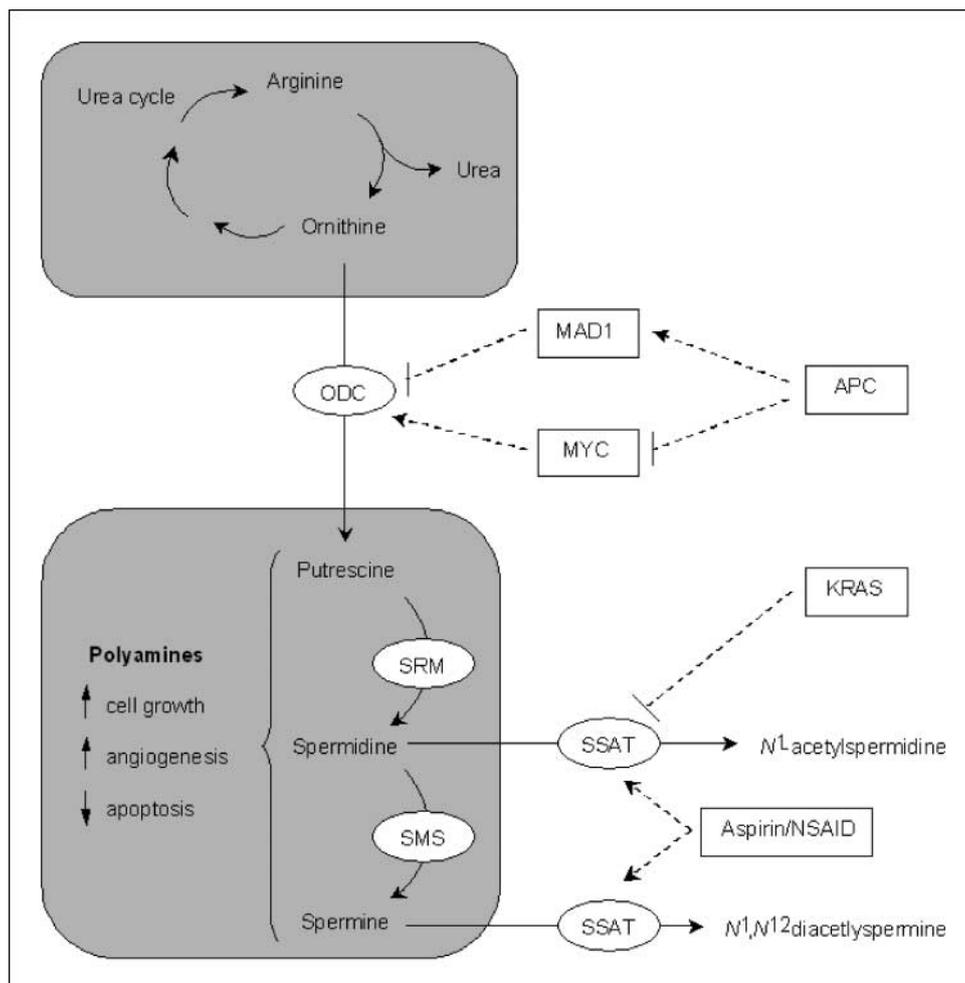
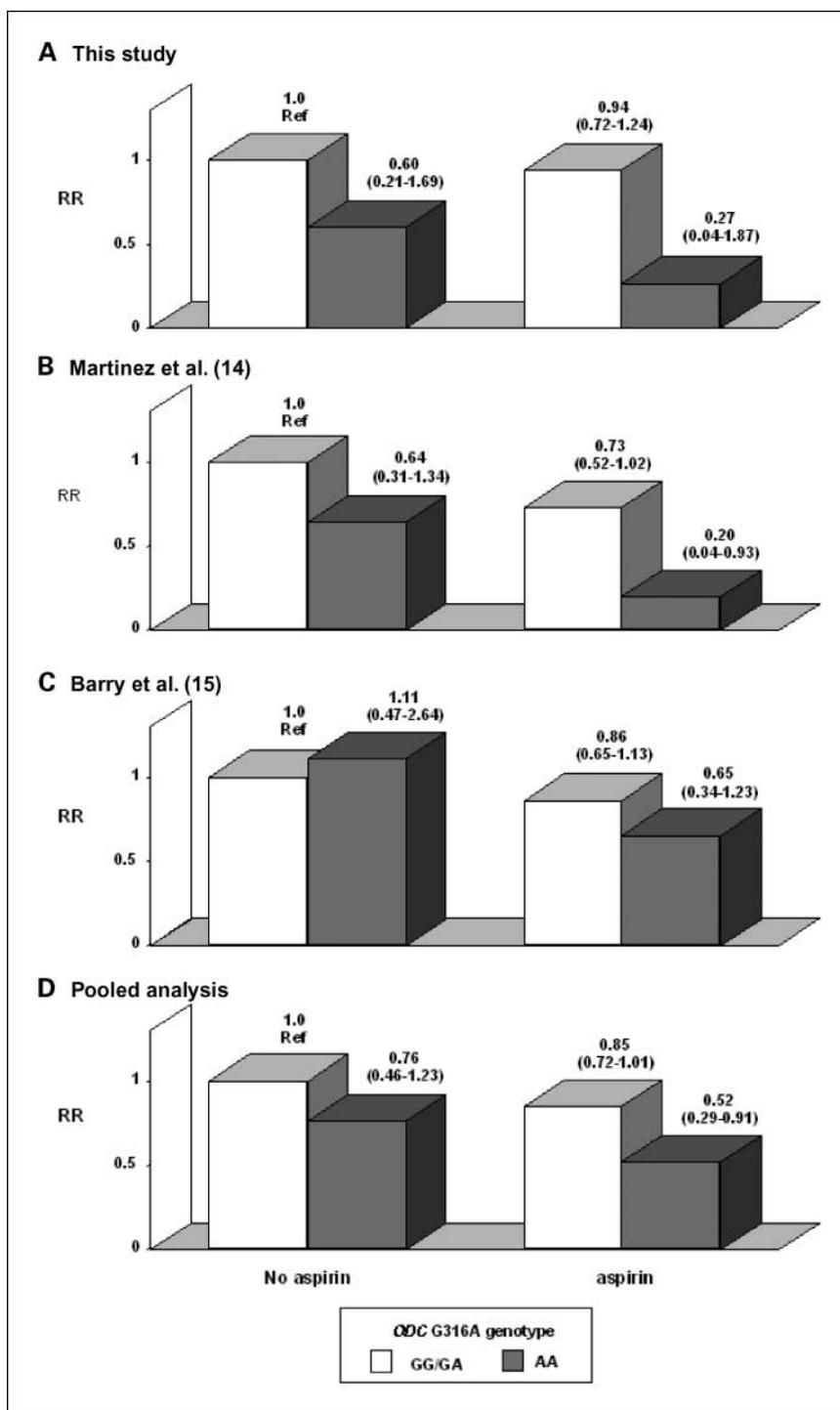


Fig. 1. A schematic representation of polyamine metabolism. The metabolism of arginine in the urea cycle results in ornithine production. ODC catalyzes the first step in polyamine synthesis in which ornithine is decarboxylated to produce putrescine. Spermidine synthase (*SRM*) converts putrescine to spermidine, which is subsequently converted to spermine by spermine synthase (*SMS*). SSAT acetylates spermidine and spermine, which are then either converted back to putrescine or exported from the cell and excreted in urine. Wild-type APC suppresses *ODC* gene expression through stimulation of MAD1 and inhibition of MYC. Aspirin and other NSAIDs induce SSAT transcription, whereas KRAS inhibits SSAT transcription.

Fig. 2. RRs and 95% CIs for adenoma recurrence stratified by *ODC* G316A genotype and aspirin exposure in this study (A), Martinez et al. (B), Barry et al. (C), and pooled analysis (D). In each panel, the reference group is individuals with either *ODC* 316GG or 316AA genotypes who were not exposed to aspirin. For B and C, RRs and 95% CIs were calculated from published raw data without adjustment.



Both aspirin and NSAIDs inhibit the prostaglandin H synthase 2 (PTGS2; or cyclooxygenase-2) enzyme, and this inhibition is thought to be responsible for some of their anti-neoplastic properties (21). Experiments in human colon cancer cells, however, have shown that NSAIDs can induce apoptosis in cells that do not express PTGS2 (22). Furthermore, some NSAID metabolites that do not inhibit PTGS2 can suppress colon tumor growth in rodents, providing additional evidence for chemopreventive properties independent of PTGS2 inhibition (23). Aspirin and other NSAIDs

induce expression of spermidine/spermine *N*¹-acetyltransferase (SSAT), an enzyme involved in polyamine catabolism (Fig. 1), and NSAID-induced apoptosis can be reversed in part by exogenous polyamines, indicating a causal role for SSAT induction and polyamine catabolism in NSAID-induced apoptosis (7, 24). Expression of SSAT is negatively regulated by the *KRAS* oncogene, which is commonly affected by activating mutations in human colon and other gastrointestinal cancers (25). Collectively, these data support a model in which a proportion of the antineoplastic effects of aspirin in

colorectal neoplasia are mediated through SSAT induction and reduced polyamine levels.

The functional nature of the *ODC* G316A polymorphism has been documented with allele-specific responses to both activators and suppressors of transcription (13, 14). In a human colon cancer cell line, the activity of the *ODC* promoter containing the A allele was selectively suppressed in a *MAD1*-dependent manner (14). This supports the recessive mode of action observed in our study because the presence of either one or two G alleles would be sufficient to block *MAD1* binding and facilitate increased *ODC* promoter activity and polyamine synthesis.

More than 90% of sporadic CRAs acquire somatic mutations in the *APC* gene and show defects in *APC*-dependent signaling (26). Wild-type *APC* suppresses the transcription factor *MYC* and activates the *MYC* antagonist *MAD1* (27). The *ODC* gene is a target of both *MYC* and *MAD1*, and *MYC* activates *ODC* transcription whereas *MAD1* is a suppressor; thus, increased *ODC* expression will occur following loss of wild-type *APC* function (12, 14). Support for this comes from studies that show that wild-type *APC* suppresses *ODC* expression in a *MYC*-dependent manner in human colon tumor cells (27), and increased *ODC* expression occurs in the normal colonic mucosa of individuals with familial adenomatous polyposis (FAP), a Mendelian CRC susceptibility syndrome caused by germ-line mutations in the *APC* gene (28). These data indicate a role for increased *ODC* expression and altered polyamine levels in *APC*-dependent colonic carcinogenesis.

Nicotine may increase *ODC* enzyme activity (29), and a previous study has reported evidence that the *ODC* G316A polymorphism may interact with cigarette smoking to influence prostate cancer risk (30). In this nested case-control study,

genotype did not significantly influence risk directly, but individuals with one or two A alleles were at increased prostate cancer risk if they were also current smokers. In our study, smoking did not influence risk of CRA recurrence or modify the association between *ODC* G316A genotype and recurrence (data not shown).

Regular aspirin use increases the incidence of gastrointestinal bleeding in a dose-dependent manner and also increases the incidence of hemorrhagic stroke (31, 32). A meta-analysis of 21 randomized trials comparing aspirin with placebo reported pooled odds ratios of between 1.5 and 2.0 for different categories of gastrointestinal bleeding, such as hematemesis and melena, although fatal bleeds were very rare, and the risks of peptic ulceration and upper gastrointestinal symptoms were also increased (pooled odds ratios, 1.3 and 1.7, respectively; ref. 31), whereas a separate meta-analysis of 16 randomized trials found that aspirin treatment was associated with a significantly elevated absolute risk of hemorrhagic stroke of 12 events per 10,000 persons (32). Although cyclooxygenase-2-selective NSAIDs are associated with a reduction in gastrointestinal adverse effects, they also result in an increase in cardiovascular events, precluding their use in primary or secondary prevention of colorectal neoplasia (33–35). *ODC* 316A genotype has the potential to identify individuals predisposed to gain differential benefit from aspirin for colorectal neoplasia chemoprevention, resulting in a favorable change in the risk-benefit ratio.

In summary, data from our own study and two independent randomized trials indicate that homozygosity for the *ODC* 316A allele is prognostic for CRA recurrence, and genotype is also predictive of the chemopreventive efficacy of aspirin, giving this variant the potential to be a clinically useful marker.

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