

Calcium, Vitamin D, and Risk for Colorectal Adenoma: Dependency on Vitamin D Receptor *BsmI* Polymorphism and Nonsteroidal Anti-Inflammatory Drug Use?¹

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Abstract

Previous epidemiological studies have been inconclusive in demonstrating an inverse association among calcium, vitamin D, and risk for colorectal adenoma. The purpose of this analysis was to evaluate the associations among calcium and vitamin D and risk for incident, sporadic colorectal adenoma according to the vitamin D receptor *BsmI* polymorphism and nonsteroidal anti-inflammatory drug (NSAID) use. We analyzed data from a colonoscopy-based case-control study ($n = 177$ cases, 228 controls) conducted in North Carolina between 1995 and 1997. Adjusted odds ratios (ORs) comparing participants in the highest to those in the lowest tertiles of total calcium and vitamin D intakes were 0.64 [95% confidence interval (CI), 0.35–1.15], $P_{\text{trend}} = 0.14$ and 0.69 (95% CI, 0.41–1.18), and $P_{\text{trend}} = 0.19$, respectively. Adjusted ORs for those in the upper tertile of total calcium intake relative to those in the lower were 0.25 (95% CI, 0.08–0.80) among those who had a Bb genotype, 0.57 (95% CI, 0.18–1.82) among those who had a bb genotype, and 0.36 (95% CI, 0.15–0.85) among those who did not take NSAIDs. The ORs for the highest tertile of calcium intake was 0.05 (95% CI, 0.01–0.41), $P_{\text{trend}} < 0.01$ among those who were Bb and did not take NSAIDs, and 0.16 (95% CI, 0.02–1.36), $P_{\text{trend}} = 0.47$ among those who were bb and did not take NSAIDs.

These data support the hypotheses that higher calcium intakes may decrease risk for colorectal neoplasms, and that such a relationship is more readily detectable among those who do not take NSAIDs, and may be strongest among those who have at least one vitamin D receptor *BsmI* b allele.

Introduction

Colorectal cancer is the second leading cause of cancer mortality in the United States, and affects men and women virtually equally (1). Calcium may be important to colorectal carcinogenesis because of its ability to bind toxic bile acids, rendering them inert, or by its direct effects on the cell cycle (2–9). The role of calcium in colon cancer etiology is linked to vitamin D, because the active metabolite of vitamin D, 1,25(OH)₂D₃³ mediates intestinal calcium absorption. In addition to its indirect role in maintaining calcium homeostasis, the direct genomic action of vitamin D is linked to a multitude of biological responses, including DNA synthesis and preventing double-strand breaks by exogenous or endogenous sources, making vitamin D an important independent contributor to the calcium/colorectal carcinogenesis mechanistic pathway.

Despite the biological plausibility, epidemiological studies have been inconsistent, although somewhat supportive of a modest reduction in risk with higher intakes of calcium and vitamin D (10–42). On the other hand, a growing number of laboratory and animal studies indicate that calcium and vitamin D may protect against risk for colorectal neoplasia, and a large, randomized, double-blind, placebo-controlled adenoma recurrence trial of calcium supplementation found a statistically significant 15% reduction in adenoma recurrence with calcium supplementation (10). *In vitro* studies show that calcium and 1,25(OH)₂D₃ inhibit cell proliferation (43–45), induce cell differentiation (46, 47), and stimulate apoptosis (48) in a variety of cell lines. The actions of 1,25(OH)₂D₃ are mediated by a ligand-induced transcription factor, the nuclear VDR (3).

Thus, although biologically plausible mechanisms exist, and basic science, animal studies, and a randomized, double-blind, placebo-controlled clinical trial strongly support anticarcinogenic activity, only weak or inconsistent associations have been observed in observational epidemiological studies of calcium, vitamin D, and risk for colorectal cancer. We hypothesized that VDR polymorphisms may modulate the association among calcium, vitamin D, and colorectal

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³ The abbreviations used are: 1,25(OH)₂D₃, 1,25-dihydroxycholecalciferol; VDR, vitamin D receptor; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; CI, confidence interval; FFQ, food frequency questionnaire.

Table 1 Selected characteristics of study population, Markers for Adenomatous Polyps case-control study, 1995–1997

Characteristic ^a	Adenoma cases (n = 177)	Controls (n = 228)	P ^b
			Adenoma cases vs. controls
Demographics			
Age (yrs)	58.4 (8.4)	56.0 (10.0)	0.02
Female (%)	39.5	64.0	0.001
College graduate (%)	20	23.2	0.43
White race (%)	88.6	90.2	0.61
Family history			
1° Relative with colon cancer (%)	20.0	35.5	0.001
Lifestyle/body size			
Physical activity (METs/day)	50.3 (16.1)	51.5 (13.6)	0.27
Current cigarette smoker (%)	31.0	19.7	0.01
Currently drink alcohol (%)	52.9	42.5	0.01
Body mass index (kg/m ²)	27.2 (5.3)	27.3 (5.9)	0.84
Take NSAIDs (%)	47.5	53.9	0.20
Dietary intakes			
Dietary fiber (gm/day)	22.7 (9.3)	23.8 (10.9)	0.14
Total fat (gm/day)	72.4 (39.6)	67.2 (33.1)	0.67
Total energy intake (kcal/day)	2,040 (812)	1,999 (788)	0.66
Total fruit and vegetables (servings/wk)	6.2 (3.5)	6.5 (3.9)	0.55
Total calcium (mg/day)	746 (405)	826 (451)	0.06
Dietary calcium (mg/day)	677 (337)	689 (328)	0.35
Supplemental calcium (mg/day)	70 (208)	136 (296)	0.04
Total vitamin D (IU/day)	314 (256)	346 (300)	0.17
Dietary vitamin D (IU/day)	205 (122)	202 (115)	0.72
Supplemental vitamin D (IU/day)	109 (223)	144 (261)	0.17
VDR <i>BsmI</i> Genotype (%)			
BB	28.9	25.9	
Bb	37.2	37.3	
bb	34.0	36.8	0.79

^a Continuous variables presented as mean (\pm SD); categorical variables as proportions in percent.

^b For continuous variables, based on analysis of covariance for age- and sex-adjusted mean differences, and for categorical variables, based on χ^2 test (exceptions: age variable adjusted only for sex, and sex variable adjusted only for age).

adenoma and, additionally, that reduced risk from NSAID use may be so overwhelming that any association with calcium and vitamin D would be masked among those who use NSAIDs on a regular basis. To date, three epidemiological studies (49–51) have evaluated the association between VDR polymorphisms and risk for colorectal adenoma, and one previous study has investigated the association between VDR polymorphisms and risk for colorectal cancer (52). Of the two adenoma studies that considered the *BsmI* polymorphism, one (49) reported a potential interaction among *BsmI* genotype, calcium, and vitamin D, and the other (51) reported no overall association between *BsmI* genotype and risk for adenoma. To clarify these inconsistencies, the purpose of this analysis is to evaluate associations among calcium and vitamin D and risk for incident sporadic colorectal adenomatous polyps according to VDR *BsmI* polymorphism and NSAID use using data from a colonoscopy-based case-control study in a North Carolina population of men and women.

Materials and Methods

Study Population. Participants for this case-control study were recruited from patients who were scheduled for a colonoscopy visit by community gastroenterology practices in Winston-Salem and Charlotte, North Carolina. All of the self-reported information, including medical history and dietary history, was obtained before case/control status was determined.

Eligibility criteria included no previous adenoma, no in-

dividual history of cancer (except nonmelanoma skin cancer), no known genetic syndromes associated with colonic neoplasia (familial polyposis or Gardner's syndrome), no history of ulcerative colitis or Crohn's disease, resident of the Winston-Salem or Charlotte, North Carolina metro areas, English speaking, and 30–74 years of age.

Cases were defined as patients with at least one adenomatous polyp and controls were those patients without adenomatous polyps. Each polyp removed at colonoscopy was examined by an index pathologist using diagnostic criteria adopted from the National Polyp Study (53). Information regarding location, size, shape, polyp type, adenoma subgroup, and degree of dysplasia was recorded.

The participation rate among all of the colonoscoped patients was 63%. Among the participants, 184 had adenomatous polyps, and 236 subjects were adenoma free at colonoscopy. Of these, 15 ($n = 7$ cases and $n = 8$ controls) were excluded for: (a) implausible total energy intake (<500 kcal/day or >6000 kcal/day) on the FFQ ($n = 2$ cases and $n = 6$ controls); (b) total number of blank items exceeded 15 on the FFQ ($n = 3$ cases and 1 control); or (c) incomplete medical history information ($n = 2$ cases and $n = 1$ control). Thus, a total of 177 cases and 228 control participants were included in this analysis.

Dietary Assessment. An adaptation of the Willett semiquantitative FFQ (153 items), expanded to include additional vegetables, fruit, and low-fat foods was administered. Study participants also provided information on medical history,

smoking habits, alcohol intake, physical activity, reproductive history (women), family history of cancer, and anthropometrics.

Specific questions in the FFQ regarding calcium and vitamin D supplement use assessed current multiple vitamin use, frequency of multiple vitamin use, and dose and frequency of calcium and vitamin D supplements. Average daily nutrient intake from dietary (*versus* supplemental) sources in the FFQ was assessed as the average daily intake over the past 12 months. In addition, the brand of multivitamin and individual vitamin supplements was recorded. Total calcium intake and total vitamin D intake was calculated as the sum of dietary and supplemental intakes.

Study participants provided specific information regarding whether they regularly took an NSAID (defined as taking an NSAID once a week or more), and if so, the frequency and duration. Similar information was also collected separately for aspirin.

Genotyping. Blood samples were drawn, processed, and stored as nuclear pellets for subsequent DNA extraction to determine genotype status. PCR was used to amplify the 825-bp *BsmI* polymorphic site fragment in intron 8 (54). The PCR product was digested with *BsmI* at 65°C and then electrophoresed on 2% agarose gels. Restriction enzyme digestion resulted in two fragments, 650-bp and 175-bp, when the *BsmI* site was present. The resulting alleles were designated B (restriction site absent) or b (restriction site present), producing three possible genotypes: BB, Bb, and bb.

Statistical Analysis. Standard techniques for case-control analyses were used. Age- and sex-adjusted mean baseline characteristics were computed for cases and controls using analysis of covariance for continuous variables and χ^2 tests for categorical variables. The OR was the measure of association. For all of the ORs, 95% CI was calculated. Unless indicated otherwise, vitamin D and calcium intakes were categorized into sex-specific tertiles based on FFQ data among controls. Unconditional multivariate logistic regression models were used to obtain final estimates. Test for trend was based on the median of each category of nutrient intake.

Effect modification was assessed by comparing stratum-specific ORs (for continuous variables, the potential effect modifier was dichotomized at the median). Subsequently, confounding factors were assessed. The basis for the assessment of confounding factors included: (a) biological plausibility; (b) whether the variable of interest was associated with outcome and exposure; and (c) whether the regression coefficient of the exposure variable of interest substantially changed after adding the potential confounding variable. Potential confounders considered in this analysis were practice site, age, race, sex, total energy intake, NSAID use, education, family history of colon cancer, physical activity, smoking status (current, ever, or never), body mass index, waist: hip ratio, and intakes of total fat and total fruits and vegetables. Final covariates included in multivariate-adjusted models were age, sex, and total energy intake.

Results

Selected characteristics of cases and controls are shown in Table 1. On average, cases were older, more likely to be male, less likely to have a first-degree relative with colon cancer, more likely to be a current smoker or to currently drink alcohol, and consumed, on average, less total calcium when compared with their control counterparts. Neither total vitamin D consumption, including dietary and supplemental vitamin D, nor the distribution of VDR *BsmI* genotypes differed substantially

Table 2 Multivariate-adjusted associations of total calcium intake, total vitamin D intake, VDR *BsmI* genotype, and NSAID use; Markers for Adenomatous Polyps case-control study, 1995–1997

Risk factor	Age-, sex-, and energy-adjusted associations; OR (95% CI) ^a
Total calcium intake ^b	
Low	1.00 (referent)
Medium	0.95 (0.57 to 1.58)
High	0.64 (0.35 to 1.15)
<i>P</i> _{trend}	0.14
Total vitamin D intake ^b	
Low	1.00 (referent)
Medium	1.10 (0.66 to 1.81)
High	0.69 (0.41 to 1.18)
<i>P</i> _{trend}	0.19
VDR genotype	
BB	1.00 (referent)
Bb	0.89 (0.55 to 1.46)
bb	0.87 (0.53 to 1.45)
Bb + bb	0.88 (0.58 to 1.36)
NSAID use	
No	1.00 (referent)
Yes	0.73 (0.48 to 1.11)

^a OR (95% CI).

^b Sex-specific tertile ranges (median) for total calcium (mg/day) intake among males: low: 0–570 (434), medium: 571–857 (683), high: 858–2015 (1175); among females: low: 0–552 (407), medium: 553–928 (701), high: 929–2857 (1288). Total Vitamin D intake (IU/day) among males: low: 0–175 (116), medium: 176–356 (242), high: 357–2302 (576); among females: low: 0–158 (106), medium: 159–433 (241), high: 434–1656 (612).

between cases and controls. The frequency of having at least one B allele was 47.5% among cases and 44.6% among controls. Similarly, the frequency of having at least one b allele was 52.5% among cases and 55.4% among controls. The control population was drawn from three different gastroenterology practices. Within each practice, the control population was in Hardy-Weinburg equilibrium.

Characteristics of adenomas in cases included: 60% had multiple polyps, 36% had adenomas >1 cm in greatest diameter, 92% had only tubular polyps, 49% had moderate/severely dysplastic adenoma, 70% had sessile polyps, and 81% of polyps were located in the colon only (data not shown).

Age-, sex-, and total energy-adjusted associations for calcium intake, vitamin D intake, VDR *BsmI* genotype, and NSAID use are shown in Table 2. There were estimated approximate one-third reductions in risk for adenomas for participants in the highest *versus* lowest tertiles of total calcium intake and vitamin D intake, although the findings were not statistically significant. Associations for the various VDR genotypes and adenoma risk were close to 1.0. There was an estimated 27% reduction in risk for those who took NSAIDs on a regular basis; however, this finding was not statistically significant.

Because vitamin D mediates intestinal calcium absorption, we additionally explored whether the association between calcium and colorectal adenoma risk differed according to levels of total vitamin D intake. No evidence for an interaction, multiplicative or additive, was found (data not shown).

Adjusted ORs for the calcium/colorectal adenoma association and the vitamin D/colorectal adenoma association stratified by genotype status are shown in Table 3. Stratification by genotype suggested a statistically significant, substantially decreased risk for adenoma with high calcium intake among those with at least one b allele. There was no consistent risk pattern across tertiles of vitamin D intake within levels of genotype or

Table 3 Age-, sex-, and energy-adjusted associations of total calcium intake, total vitamin D intake, and risk for adenomatous polyps, stratified by NSAID use and VDR genotype; Markers for Adenomatous Polyps case-control study, 1995–1997

	Low OR (95% CI)	No. of cases	Medium OR (95% CI)	No. of cases	High OR (95% CI)	No. of cases	P_{trend}
Total calcium intake (tertiles)							
VDR genotype							
BB	1.00 (referent)	14	2.03 (0.68 to 6.12)	19	0.81 (0.24 to 2.74)	12	0.62
Bb	1.00 (referent)	22	0.41 (0.15 to 1.11)	22	0.25 (0.08 to 0.80)	14	0.02
bb	1.00 (referent)	21	1.38 (0.58 to 3.28)	24	0.57 (0.18 to 1.82)	8	0.47
NSAID use							
No	1.00 (referent)	42	0.79 (0.38 to 1.63)	31	0.36 (0.15 to 0.85)	20	0.63
Yes	1.00 (referent)	25	1.53 (0.72 to 3.24)	36	1.26 (0.52 to 3.04)	23	0.01
Total vitamin D intake (tertiles)							
VDR genotype							
BB	1.00 (referent)	14	2.12 (0.67 to 6.67)	20	1.37 (0.35 to 5.35)	11	0.77
Bb	1.00 (referent)	29	0.39 (0.15 to 1.04)	16	0.29 (0.09 to 0.95)	13	<0.01
Bb	1.00 (referent)	14	2.35 (0.80 to 6.50)	24	2.25 (0.74 to 6.88)	15	0.65
NSAID use							
No	1.00 (referent)	39	1.26 (0.59 to 2.70)	35	1.26 (0.48 to 3.26)	19	0.42
Yes	1.00 (referent)	25	1.51 (0.69 to 3.29)	34	0.84 (0.35 to 2.01)	25	0.39

Table 4 Multivariate-adjusted^a associations of total calcium intake and risk for adenomatous polyps jointly stratified by NSAID use and VDR genotype; Markers for Adenomatous Polyps case-control study, 1995–1997

	Total calcium intake (tertiles)						P_{trend}
	Low OR (95% CI)	No. of cases	Medium OR (95% CI)	No. of cases	High OR (95% CI)	No. of cases	
NSAID users							
BB	1.00 (referent)	6	0.87 (0.22 to 3.48)	9	0.68 (0.22 to 3.48)	8	0.54
Bb	1.00 (referent)	10	0.72 (0.18 to 2.87)	12	0.39 (0.07 to 2.13)	7	0.41
bb	1.00 (referent)	9	2.04 (0.41 to 10.22)	14	1.66 (0.31 to 8.84)	4	0.74
NSAID nonusers							
BB	1.00 (referent)	8	1.91 (0.55 to 6.63)	10	0.58 (0.13 to 2.61)	4	0.13
Bb	1.00 (referent)	12	0.11 (0.02 to 0.67)	10	0.05 (0.01 to 0.41)	7	<0.01
bb	1.00 (referent)	12	2.18 (0.40 to 11.85)	10	0.16 (0.02 to 1.36)	4	0.47

^a Adjusted for age, sex, and total energy intake.

according to NSAID status. Although there was a statistically significant decreased risk for adenoma among those with the Bb genotype, the overall pattern across genotype was not consistently in a direction of decreased risk with increasing total vitamin D intake.

Use of NSAIDs modified the association between calcium intake and risk for adenoma (Table 3). The data suggest a substantially lower risk for adenoma among those in the highest tertile of calcium intake who did not take NSAIDs [multivariate-adjusted OR comparing those in the highest to lowest tertile of total calcium intake was 0.36 (95% CI, 0.15–0.85)], whereas this reduction in risk was not apparent among those who took NSAIDs on a regular basis [multivariate-adjusted OR comparing those in the highest to lowest tertile of calcium intake was 1.26 (95% CI, 0.52–3.04)]. There were no distinct differences in the vitamin D-adenoma association according to NSAID use.

In a subgroup analysis, to additionally investigate patterns of risk across NSAID use and genotype status, risk estimates jointly stratified on these two variables are presented for the calcium/colorectal adenoma association in Table 4. The inverse calcium-adenoma association was strongest among participants who did not use NSAIDs on a regular basis and who had at least one b allele. The adjusted ORs comparing the highest to lowest tertile of calcium intake among those who did not use NSAIDs regularly and who had either the Bb genotype or bb genotype were, respectively, 0.05 (95% CI, 0.01–0.41) and 0.16 (95% CI, 0.02–1.36).

Discussion

These data support the hypothesis that higher calcium intake decreases risk for sporadic adenoma. The inverse calcium-adenoma association was most readily detectable among participants who did not take NSAIDs on a regular basis. Furthermore, the calcium-colorectal adenoma association varied according to *BsmI* genotype such that participants with at least one b allele were at much lower risk for colorectal adenoma. These data do not support a strong association between increased vitamin D consumption and risk for sporadic adenoma, nor do they indicate a difference in the vitamin D/colorectal cancer association across *BsmI* genotypes or NSAID use.

Important strengths of this study include: (a) the control group underwent colonoscopy and was known to be adenoma negative; (b) all of the self-report information (including dietary questionnaire) was determined before case-control status was known, thus minimizing recall bias; (c) detailed information on supplemental vitamin D and calcium intake, including dose and brand of supplement, was collected; and (d) detailed information on other potential confounding factors, such as medical history, multivitamin use, and dose and frequency of NSAID use, was collected.

As with most studies investigating gene-environment interactions, the main limitation to this study is its small sample size. Considering the small sample size, the genotype findings may be attributable strictly to chance. However, the pattern of

findings is consistent with biologically plausible *a priori* hypotheses. Because the study population was drawn from individuals who underwent colonoscopy, results from this analysis may not be representative of the general population. Furthermore, dietary information was collected based on current diet within 1 year before colonoscopy. If calcium and vitamin D are important early on in the carcinogenesis process, and previous dietary intake differs significantly from current dietary intake among cases and controls, then a nondifferential bias is expected, which would attenuate results. In this study, information regarding vitamin D intake was solely based on FFQ data. Information on sun exposure, a potentially important source of vitamin D, was not collected. Because cases and controls would be misclassified equally on sunlight exposure, this type of nondifferential bias is expected to bias the estimated OR toward the null.

Analytic epidemiological studies (11–38) have suggested a modest reduction in risk for colon cancer with higher calcium intakes; however, they have not been convincingly consistent. Only one intervention study has investigated the effects of calcium supplementation on risk for adenoma recurrence (10). This large, well-conducted, randomized, double-blind, placebo-controlled clinical trial found an adjusted risk ratio for any recurrence of adenoma with calcium compared with placebo of 0.85 (95% CI, 0.74–0.98).

Fewer studies have investigated the association among calcium, vitamin D, and colorectal adenoma (32, 38–41). A combined analysis of cohort data from the Nurse's Health Study and Health Professionals Follow-Up Study (39) found that calcium was inversely associated with colorectal adenoma, although this finding was not statistically significant. The same study reported a nonsignificant, inverse association with increasing vitamin D intake among women. In addition to the prospective studies, at least three previous case-control studies (32, 40, 41) have investigated calcium and/or vitamin D as independent risk factors for sporadic colorectal adenoma. In general, results from these studies have suggested unconvincing inverse associations. Our findings of weak, nonsignificant associations among calcium, vitamin D, and risk for colorectal adenoma are similar to those of previous adenoma case-control studies that did not take into account NSAID use or differences according to VDR genotype. However, our results have additionally indicated that the association between calcium and risk for colorectal adenoma may be modulated by polymorphisms in the VDR and that a true relationship may be masked by NSAID use.

Although observational data are only weakly supportive of a reduced risk for colorectal cancer with increasing intake of calcium and vitamin D, biologically plausible mechanisms of action and animal data strongly support the role of calcium and vitamin D in reducing risk for colorectal carcinogenesis (55). In addition to the postulated protective effect of calcium against colon carcinogenesis because of its ability to bind bile acids in the gut, *in vitro* data show that calcium directly affects the cell cycle, modulating cell proliferation and differentiation (5–7, 56). Vitamin D is thought to be important in regulating DNA replication, differentiation, and apoptosis (56–58). Thus, the hypothesized effects of vitamin D independent of its role in calcium homeostasis may contribute to decreasing risk for colorectal carcinogenesis.

Because the majority of known effects of vitamin D are mediated through a genomic pathway via the VDR, and vitamin D mediates calcium homeostasis, polymorphisms in the VDR may modulate the effects of calcium on colorectal carcinogenesis. The VDR is a member of the steroid/thyroid receptor

family, and is expressed in normal and malignant colon cells (59). Polymorphisms in the 3' untranslated region of the VDR gene, including the RFLP restriction sites in intron 8 (*BsmI* and *ApaI*) and exon 9 (*TaqI*), were reported to be in strong linkage disequilibrium in Caucasians, resulting in two common haplotypes, Bat and baT (56). Thus, *BsmI* polymorphism may be in linkage disequilibrium with another polymorphism that affects VDR function. Alternatively, it has been shown that these polymorphisms in the 3' untranslated region of the VDR gene alter transcriptional activity and mRNA stability in minigene reporter constructs (59). In this way, the VDR *BsmI* polymorphism may influence colorectal cancer risk via a pathway that influences the level of VDR mRNA. Recent molecular epidemiological studies found that various VDR polymorphisms are associated with prostate cancer, breast cancer, and malignant melanoma (60–62).

Thus far, three previous case-control studies have investigated the association between calcium and vitamin D intake, polymorphisms in the VDR receptor, and risk for colorectal adenoma (49–51). One of these studies included NSAID use in the final multivariate-adjusted model; however, none of these studies investigated the potential modifying role of NSAID use. Studies of VDR polymorphisms and adenoma risk have not been entirely consistent, and this may be partially because of the role of NSAID use as a modifier of the association between calcium and vitamin D intake and colorectal adenoma risk.

In summary, our findings of modest, inverse associations of increasing calcium and vitamin D intakes and risk for colorectal adenoma are similar to those estimates reported in previous observational epidemiological studies. However, this study adds to the previous literature by showing that the inverse calcium-adenoma association is most readily detectable (substantial and statistically significant) among those participants who did not take NSAIDs on a regular basis, a finding that may explain inconsistencies in previous epidemiological studies investigating the calcium-colorectal adenoma association. Furthermore, our observation that the calcium-colorectal adenoma association varied according to *BsmI* genotype such that participants with at least one b allele were at substantially lower risk for colorectal adenoma is also new, and as yet unconfirmed by other epidemiological findings. The consistency of these findings with animal and laboratory data, and the results of a randomized, placebo-controlled trial of calcium supplementation and adenoma recurrence, provides additional support and mechanistic clues for the hypothesis that higher calcium intakes, perhaps particularly among persons of certain genetic makeups, may reduce risk for colorectal neoplasms.

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