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# Polymorphisms in genes related to inflammation and obesity and colorectal adenoma risk

**Brian Z. Huang**[1,2,3], **Konstantinos K. Tsilidis**[4,5], **Michael W. Smith**[6], **Judith Hoffman-Bolton**[1], **Kala Visvanathan**[1,7,8], **Elizabeth A. Platz**[1,8,9], **Corinne E. Joshu**[1,7,8]

[1]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland [2]Department of Epidemiology, UCLA Fielding School of Public Health, Los Angeles, California [3]Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, California [4]Department of Hygiene and Epidemiology, School of Medicine, University of Ioannina, Ioannina, Greece [5]Department of Epidemiology and Biostatistics, The School of Public Health, Imperial College London, London, United Kingdom [6]Division of Genome Sciences, Extramural Research Program, National Human Genome Research Institution, Bethesda, Maryland [7]Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland [8]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland [9]James Buchanan Brady Urological Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland

## Abstract

We previously investigated the association between single nucleotide polymorphisms (SNPs) in genes related to obesity and inflammation and colorectal cancer in the CLUE II cohort. However, the relationships between these SNPs and colorectal adenomas have not been well evaluated. In a nested case-control study of 135 incident adenoma cases and 269 matched controls in the CLUE II cohort (1989–2000), we genotyped 17 candidate SNPs in 12 genes (*PPARG, TCF7L2, ADIPOQ, LEP, IL10, CRP, TLR4, IL6, IL1B, IL8, TNF, RNASEL*) and 19 tagSNPs in three genes (*IL10, CRP,* and *TLR4)*. Conditional logistic regression was used to calculate odds ratios (OR) for adenomas (overall and by size, histology, location, number). Polymorphisms in the inflammatory-related genes *CRP, ADIPOQ, IL6,* and *TLR4* were observed to be associated with adenoma risk. At rs1205 in *CRP,* T (minor allele) carriers had a higher risk (OR 1.67, 95%CI 1.07–2.60; reference: CC) of adenomas overall and adenomas with aggressive characteristics. At rs1201299 in *ADIPOQ,* the AC genotype had a higher risk (OR 1.58, 95%CI 1.00–2.49) of adenomas, while the minor AA genotype had a borderline inverse association (OR 0.44, 95%CI 0.18–1.08; reference: CC). At rs1800797 in *IL6,* the AA genotype had a borderline inverse association (OR 0.53, 95%CI 0.27–1.05; reference: GG). Three TLR4 tagSNPs (rs10116253, rs1927911, rs7873784) were associated with adenomas among obese participants. None of these SNPs were associated with colorectal cancer in our prior study in CLUE II, possibly suggesting a different genetic etiology for early colorectal neoplasia.

**Correspondence** Brian Z. Huang, MPH, Department of Research & Evaluation, Kaiser Permanente Southern California, 100 S. Los Robles Ave, Pasadena, CA 91101. brian.huang@kp.org.

**Keywords**

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## 1 | INTRODUCTION

Obesity is an established risk factor for colorectal neoplasia and has been postulated to promote cancer development through inflammation-related mechanisms.[1,2] This hypothesis has been explored by numerous epidemiologic studies evaluating circulating markers of inflammation and colorectal cancer and adenomas. Several meta-analyses have suggested an increased colorectal cancer risk with higher serum levels of the proinflammatory cytokines interleukin-6 (IL-6)[3] and C-reactive protein (CRP),[4] and a decreased risk with higher concentrations of the anti-inflammatory adipokine adiponectin.[5] Additionally, serum levels of the anti-inflammatory and immunosuppressive interleukin-10 (IL-10) have been reported to be elevated among adults with colorectal cancer in some,[6–8] but not all,[9] small case-control studies. In regards to adenoma risk, studies have detected inverse associations for adiponectin[10] and mainly null associations for CRP[11–14] serum concentrations, whereas findings for IL-6,[12,14–16] and IL-10[15,16] serum levels have been more inconsistent.

As serum marker expression is, in part, under genetic control, several studies have evaluated the relationships between common single nucleotide polymorphisms (SNPs) in genes associated with inflammation and obesity and the risk of colorectal neoplasia. We previously investigated the associations of SNPs in 12 inflammation- and obesity-related genes with colorectal cancer in the CLUE II cohort, where we observed that carrying the minor G allele at rs1800896 in *IL10,* which increases IL-10 production, was associated with a decreased colorectal cancer risk.[17] However, a subsequent meta-analysis that included our previous prospective study, another nested case-control and four retrospective case-control studies found no overall relationship between this SNP and colorectal cancer.[18] Evidence from meta-analyses of other SNPs supports an elevated colorectal cancer risk with the minor A allele at rs1800629 in *TNF*,[19] which increases the expression of the inflammatory tumor necrosis factor-α (TNFα),[20] and the minor G allele at rs4986790 in *TLR4*,[21] which has been found to increase cytokine levels[22] and the expression of genes linked with tumorigenesis.[23] Moreover, meta-analyses for obesity-related genes have reported greater colorectal cancer risk for the minor G allele at rs1801282 in *PPARG*,[24] which impairs the adipogenic activity of peroxisome proliferator-activated receptor gamma (PPARG),[25] but no overall associations of the minor alleles at rs1501299 on *ADIPOQ*[26] or rs7903146 on *TCF7L2*[27] with risk.

As a majority of colorectal cancers arise from adenomas, examining the influence of these SNPs on an earlier stage in the natural history of carcinogenesis may provide further insight into the etiology of colorectal cancer. There are only a few studies that have assessed the relationships between SNPs in genes involved in inflammation and obesity and the development of adenomatous polyps.[14,28,29] These studies provide evidence of an increased adenoma risk among those carrying variants associated with increased serum levels of CRP,[14] IL-8,[28] and possibly IL-1β,[28] and decreased serum levels of IL-10.[28] To continue to build

on this evidence base, we conducted a nested case-control study to evaluate the associations between candidate SNPs and tagSNPs in 12 genes related to inflammation and obesity and adenomas among participants in the CLUE II cohort. We evaluated the same SNPs that we previously analyzed in relation to colorectal cancer to determine whether the patterns of association were similar for adenomas.[17]

## 2 | MATERIALS AND METHODS

### 2.1 | Study population

We selected colorectal adenoma cases and controls from the CLUE II cohort of Washington County, Maryland and its surrounding areas. CLUE II was established to evaluate potential risk factors for cancer and cardiovascular disease. At the baseline visit in 1989, 32 894 residents donated blood specimens and completed a medical and lifestyle history questionnaire. Participants also completed a food frequency questionnaire (FFQ) at home. Follow-up occurred in 1996, 1998, and 2000 via mailed questionnaires covering lifestyle, medical, and family history information. Participants were specifically asked if they had ever received endoscopy screening of the large bowel (1996 and 2000 questionnaires) or a polyp diagnosis (all three follow-up questionnaires). For this study, we restricted the study population to the 22 887 adult residents from Washington County, MD.

### 2.2 | Colorectal adenoma cases and controls

The development of this nested case-control study has been described previously by Tsilidis et al.[17,30] Potential cases and controls consisted of individuals with no history of polyps or cancer (other than non-melanoma skin cancer or cervical cancer in situ) before 1989, and no personal history of ulcerative colitis or Crohn's disease reported on the 1996, 1998, or 2000 follow-up questionnaires.

Cases were selected from individuals that reported polyps on the 1996, 1998, or 2000 follow-up questionnaires; endoscopy and pathology reports were reviewed to confirm first ever adenomatous polyp diagnoses after 1989. Other polyp types were not included because they may carry different risks of colorectal cancer. One hundred thirty-five cases were confirmed, and classified by characteristics associated with colorectal cancer risk, including histology (tubular vs tubulovillous/villous), size (<1 vs ≥1cm), total number of adenomas (1 vs >1), and location (proximal colon, distal colon, colon, rectum). Participants who had more than one adenoma could contribute to more than one category of histology, location, and size.

Controls were selected from participants who reported a negative endoscopy after 1989 on the 1996, 1998, or 2000 follow-up questionnaires so that the controls had the same opportunity for adenoma detection (eg, self-reported endoscopy) as the cases. Two controls were randomly matched to each case based on age (±1 year), race (all cases were white), sex, date of blood draw (±1 month), and time since last meal. All controls had to be known to be alive at the time the matched case was diagnosed and not have a polyp diagnosis through the last follow-up questionnaire. Two hundred seventy controls were selected, but one was excluded from the analysis due to missing genotype data on all SNPs.

### 2.3 | SNPs

The same single nucleotide polymorphisms (SNPs) in genes related to obesity and inflammation that were evaluated by Tsilidis et al.[17] were included in the current study. These included 17 candidate SNPs in 12 genes (*IL10, CRP, TLR4, IL6, IL1B, IL8, TNF, RNASEL, PPARG, TCF7L2, ADIPOQ,* and *LEP*) and 19 tagSNPs in three genes (*IL10, CRP,* and *TLR4*). Among the 405 study participants, 404 had DNA available, and of these, 337 had genotype data on all candidate SNPs and 232 had genotype data on all tagSNPs.

SNPs were genotyped using Applied Biosystems' Taqman 5′ exonuclease assays, Taqman Universal PCR Master Mix: No AmpErase UNG, and 2.5 nanograms of genomic DNA. The thermal cycling conditions consisted of an initial hold at 95°C for 10 min followed by 50 cycles of a 15 s 92°C denature step and a one minute 60°C annealing and extension step. The 7900HT was used to detect the nucleic acids and Sequence Detection Software (SDS) v2.2 was used to discriminate alleles and call genotypes (Applied Biosystems, Foster City, CA). Additional information on genotyping procedures, SNP selection and features of each polymorphism are described in Tsilidis et al.[17]

### 2.4 | Assessment of other variables

Information on age, height, weight, smoking history, and medication use were obtained from the baseline questionnaire in 1989. We calculated BMI ($kg/m^2$) from height and weight. We classified participants as never, former, or current smokers. Participants who reported use of medications containing aspirin or non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) in the 48h prior to blood draw were classified as NSAID users. Participants who reported any use of medication to treat diabetes in the 48 h prior to blood draw were classified as diabetes medication users. Women who reported ever using hormone replacement therapy or oral contraceptives were classified as female hormone users. For participants who completed a food frequency questionnaire at baseline in 1989 (107 cases, 184 controls), we estimated daily intake of alcohol (g/day), folate (μg/day), red meat (g/day), energy (kcal/day), saturated fat (g/day), fiber (g/day), and calcium (mg/day). Information on family history of colorectal cancer was obtained from follow-up questionnaires in 1996 and 2000.

### 2.5 | Statistical analysis

To be included in the analysis, one case and at least one control of the matched set needed to have information for any given SNP. The distribution of baseline characteristics was compared across cases and controls using generalized estimating equations with exchangeable correlation structures and robust standard error estimations to account for the matched pair design of the study. Dietary measurements were natural logarithm transformed due to right skewed distributions.

For each SNP, conditional logistic regression was used to estimate the matched odds ratios (ORs) of adenoma and corresponding 95% confidence intervals (CIs) comparing heterozygous and homozygous minor genotypes to the homozygous major genotype. We tested for trend by fitting a separate model with the number of minor alleles as the independent variable. A third conditional logistic regression model was run to estimate the

OR for minor allele carrier status (heterozygous and homozygous minor genotypes combined). Because further adjustment for lifestyle factors (eg, diet, smoking, medication use) did not change the results, only findings from models that took into account the matching factors are reported. All analyses were run separately by adenoma characteristics (histology, size, location, and number of adenomas).

To evaluate effect modification, we stratified analyses by the median age (≤55 vs >55 years) and median BMI (≤26 vs >26 kg/m$^2$). We tested for potential interaction by fitting a model with a variable for minor allele carrier status, a term for either age (binary) or BMI (binary), and a product term of the two variables; we evaluated the latter term using the Wald test. Since BMI was not a matching variable, we broke the matched sets to preserve power and conducted logistic regression adjusting for the matching factors.

Hardy-Weinberg equilibrium was tested for each SNP among the controls. All genotypes were in Hardy-Weinberg equilibrium except for candidate SNPs *IL10* rs1800872 ($P = 0.01$), *CRP* rs1205 ($P = 0.05$), and *ADIPOQ* rs1501299 ($P = 0.03$). To explore whether our findings for SNPs *IL10* rs1800872, *CRP* rs1205, and *ADIPOQ* rs1501299 were influenced by deviation from equilibrium, we calculated the expected genotype frequencies for the controls using the observed control allele frequency in the Hardy-Weinberg equation. We then calculated ORs in which we compared the observed genotype distributions in the cases to the expected genotype distributions in the controls. Because these ORs did not differ from the initial analyses, we only present the ORs from the initial analysis. All analyses were two sided and were conducted using SAS version 9.3 (Cary, NC), except for the Hardy-Weinberg equilibrium tests that were performed using the genetics package in R version 3.0.2 (R Foundation for Statistical Computing).

## 3 | RESULTS

Baseline characteristics were generally similar between the cases and controls, except that cases were significantly more likely than controls to report a family history of colorectal cancer and be a former or current smoker (Table 1).

### 3.1 | Overall genotype analysis

Possible associations between genotype and colorectal adenoma risk were observed for three candidate SNPs: rs1205 in *CRP,* rs1800797 in *IL6,* and rs1501299 in *ADIPOQ* (Table 2). Carrying the T minor allele (CT and TT genotypes) at rs1205 in *CRP* was associated with a higher risk of colorectal adenomas when compared to the common CC genotype (OR 1.67,95%CI 1.07–2.60). For rs1800797 in *IL6,* there was a suggested lower risk of adenomas for the minor AA genotype compared to the major GG genotype (OR 0.53, 95%CI 0.27–1.05). Lastly, the heterozygous AC genotype of rs1501299 in *ADIPOQ* was associated with an increased risk for adenomas when compared to the major CC genotype (OR 1.58,95%CI 1.00–2.49), whereas the minor AA genotype was possibly inversely associated with risk (OR 0.44, 0.18–1.08). There were no statistically significant associations between genotype and adenomas in any of the examined tagSNPs (Table 3).

### 3.2 | Genotype analysis by adenoma characteristics

Associations between genotype and the presence of colorectal adenomas with aggressive features (eg, any villous histology, large [≥1cm], multiple adenomas [>1]) were observed for two of the CRP candidate SNPs, but none of other candidate or tagSNPs (data not shown). Carrying the T minor allele at rs1205 in *CRP* was associated with a higher risk of detecting an adenoma with any villous histology (OR 2.22, 95%CI 1.06–4.65), a large adenoma (OR 2.90, 95%CI 1.09–7.67), and >1 adenoma (OR 2.82, 95%CI 1.39–5.73). In comparison, the associations between carrying the T minor allele at rs1205 in *CRP* and adenomas with non-aggressive features were attenuated and non-significant (tubular histology: OR 1.46, 95%CI 0.88–2.41, <1 cm: OR 1.45,95%CI 0.81–2.59, and only one adenoma: OR 1.08, CI 0.59–1.97). Carrying the C minor allele at rs1800947 in CRP was associated with a higher risk of having more than one adenoma (OR 3.02, 95%CI 1.09–8.35), but not for detecting only one adenoma (OR 1.00, 95%CI 0.39–2.60). No other SNPs were significantly associated with adenomas with non-aggressive features (ie, tubular histology, <1cm, only one adenoma; data not shown).

Differences in associations between genotype and adenoma by location (eg, proximal colon, distal colon, colon, rectum) were possibly observed for two of the candidate SNPs. Carrying the T minor allele at rs1205 in *CRP* was associated with a higher risk of an adenoma in the rectum (OR 3.65, 95%CI 1.12–11.90), colon (OR 1.76, 95%CI 1.09–2.83), and distal colon (OR 2.07, 95%CI 1.09–3.93), but was not significantly associated with detecting an adenoma in the proximal colon (OR 1.54, 95%CI 0.82–2.88). Carrying the minor A allele at rs2167270 in *LEP* was associated with a higher risk of adenomas in the distal colon (OR 1.86, 95%CI 1.00–3.44) only. None of the other candidate or tagSNPs showed apparent difference by location.

### 3.3 | Genotype analysis stratified by BMI and age

When stratified by BMI, carrying the minor C allele at rs1800796 in *IL6* was positively associated with adenoma among leaner individuals (OR 4.70, 95%CI 1.56–14.20) but not among heavier individuals (OR 0.32, 95%CI 0.07–1.52; $p_{\text{interaction}}$ = 0 .01). There was also possible interaction of BMI with the minor A allele at rs1501299 in *ADIPOQ;* we observed no association among leaner individuals (OR 0.94, 95%CI 0.52–1.69), but found an increased risk of adenomas for heavier individuals (OR 1.88, 95%CI 1.00–3.54; $p_{\text{interaction}}$ = 0.10). Additionally, we observed a consistent pattern of association for minor allele carriers of all eight of the *TLR4* tagSNPs genotyped: among leaner individuals, carriers appeared to have a lower risk of adenomas compared to non-carriers, whereas among heavier individuals, carriers had an increased risk of adenomas compared to non-carriers. These interactions were statistically significant for three TLR4 tagSNPs (rs10116253, rs1927911, rs7873784; $p_{\text{interaction}}$<0.05). BMI did not modify the association for any of the other SNPs (all $p_{\text{interaction}}$>0.05).

When stratified by age, carrying the minor A allele at rs486907 in *RNASEL* was inversely associated with adenomas among younger individuals (≤55 years: OR 0.42, 95%CI 0.22–0.81), but there was no statistically significant association among older individuals (>55 years: OR 1.22, 95%CI 0.66–2.27; $p_{\text{interaction}}$ = 0.02). Furthermore, carrying the minor C

allele at rs1143627 in *IL1B* was not associated with adenomas among younger individuals (<55 years: OR 0.81, 95%CI 0.46–1.43), but was associated with an increased risk of adenomas among older individuals (>55 years: OR 1.94, 95%CI 1.02–3.71; $p_{interaction}$ = 0.06). We did not observe other differences in associations between genotype and adenoma risk by age (data not shown).

## 4 | DISCUSSION

In this nested case-control study, we evaluated the association between 17 candidate SNPs in 12 genes and 19 tagSNPs in three genes involved in inflammation and obesity and colorectal adenoma risk. The minor allele of a candidate SNP in *CRP* (rs1205) was positively associated with adenoma risk overall, and with adenomas with any villous histology, larger adenomas, multiple adenomas, and distal colon adenomas. For a candidate SNP in *ADIPOQ* (rs1501299), hetero-zygotes had an increased risk, while minor allele homozygotes had a possible decreased risk compared to major allele homozygotes. The minor homozygous genotype of a candidate SNP in *IL6* (rs1800797) had a borderline decreased risk of adenoma. BMI modified the association between several *TLR4* tagSNPs (rs10116253, rs1927911, rs7873784) and adenomas. We observed no association between *IL10* SNPs and adenomas.

C-reactive protein is an inflammatory cytokine that has been positively associated with colorectal cancer risk in prospective studies,[31] including the CLUE II cohort.[32] However, research on CRP serum levels and adenomas has produced conflicting results[11,33,34] and we found no association of serum CRP and adenomas in CLUE II.[13] We also previously reported no association between circulating CRP and the level of inflammation in normal colonic tissue measured concurrently from individuals undergoing routine screening colonoscopy.[35] Elevated circulating CRP has been hypothesized to reflect increased colonic inflammation and the immune response to colorectal neoplasia. It is possible that only more advanced colorectal carcinogenesis would produce the level of inflammation and/or immune response needed to yield detectable changes in serum levels of CRP, thereby explaining a more consistent association between CRP and colorectal cancer and prognosis than adenoma.

In the present study, the minor T allele at rs1205, which decreases *CRP* expression,[14,36] was associated with an increased risk of adenomas overall and adenomas with more aggressive characteristics (any villous histology, large size, multiple). It also appeared to be more strongly associated with adenomas in the distal colorectum than in the proximal colon. Though we expected lower adenoma risk for a SNP that reduced *CRP* expression, our observed result might instead be indicative of the protective immunosurveillance properties of CRP. As CRP is involved with the elimination of transformed and damaged cells,[37] individuals with lower CRP levels may perhaps be more likely to develop cancer precursors such as adenomas. Our findings are supported by a sigmoidoscopy-based case-control study from Hawaii, which also found an increased adenoma risk for the minor T allele at rs1205.[14] A second hospital-based case-control study, however, detected no association.[38] Moreover, we observed no association between this SNP and colorectal cancer in our prior study.[17] This is consistent with the null results for colorectal cancer observed in the prospective

Rotterdam Study from the Netherlands and a case-control nested within the European Prospective Investigation into Cancer and Nutrition.[39,40] Another study performed across multiple metropolitan regions in the United States observed no association with rectal cancer, but an increased risk for colon cancer.[41]

Adiponectin is secreted by adipose tissue and has anti-inflammatory properties such as regulation of fatty acid oxidation and cytokine production.[42] A meta-analysis of thirteen case-control and cross-sectional studies, of which three were nested case-control studies, suggested that higher circulating adiponectin levels were associated with a decreased risk of both colorectal cancer and adenomas.[10] The minor A allele of the rs1501299 SNP in *ADIPOQ* increases expression of adiponectin. In our current study, we observed that the risk of colorectal adenomas was positively associated with the heterozygous genotype and possibly inversely associated with the homozygous variant genotype. Though the positive association with the heterozygous genotype is contrary to our hypothesis, it is consistent with the borderline positive association between carriers of the minor A allele of rs1501299 and colorectal cancer risk observed in our earlier study.[17] However, a recent meta-analysis of eight case-control studies, which included our previous study as the only nested case-control, observed no overall association between the minor A allele and colorectal cancer risk.[26] To our knowledge, our present study is the only one that has evaluated rs1501299 and colorectal adenoma risk.

Interleukin-6 (IL-6) is a cytokine involved in many proinflammatory pathways of the immune response.[43] We reported a positive association between plasma IL-6 concentration and risk of colon cancer in this cohort, and presented a meta-analysis of six prospective studies that provided support for a modest positive association between IL-6 concentrations and colon cancer risk.[3] In the present study, we identified a borderline inverse association between a candidate SNP in *IL6* (rs1800797) and adenomas and, among leaner individuals only, a positive association between a different candidate SNP in *IL6* (rs1800796) and adenomas. In our prior study, we observed no significant association between these SNPs and colorectal cancer.[17] Previous studies also reported no association between rs180079[44] or rs1800796[45] and colorectal cancer risk. Given the limited existing research, more efforts are needed to further elucidate the role of *IL6* genotypes in colorectal neoplasia.

Interleukin-10 (IL-10) is a pleiotropic cytokine with immunosuppressive and antiangiogenic properties that may both promote or inhibit carcinogenesis.[8] While several small case-control studies have reported higher concentrations of IL-10 among colorectal cancer cases,[6,7] there is evidence suggesting that elevated IL-10 levels may rather be a consequence of the colorectal tumors themselves.[46] Despite an inverse association between the *IL10* rs1800896 SNP and colorectal cancer in our earlier study,[17] we did not observe any significant associations between *IL10* SNPs and adenomas. Our findings are consistent with a large case-control study of military members and families in Maryland, which yielded no link between the *IL10* rs1800896 SNP and adenomas.[28] The *IL10* rs1800896 and rs1800872 SNPs were also not associated with adenoma recurrence among participants of the Polyp Prevention Trial.[47,48] However, the rs1800896 minor allele did modify the influence of NSAIDs on recurrent adenomas among the trial participants; carriers who did not use NSAIDs had a lower risk of recurrent adenoma, while carriers who did use NSAIDs had a

higher risk of recurrence.[47] Collectively, the current literature suggests that *IL10* SNPs are perhaps more influential on later stages of colorectal carcinogenesis, and may be modified by common risk factors.

In our prior study, we reported possible inverse associations between two *TLR4* tagSNPs (rs7873784 and rs11536891) and colorectal cancer risk.[17] In the current study, *TLR4* tagSNPs were not associated with adenoma risk overall. However, among leaner individuals, minor allele carriers at all eight *TLR4* tagSNPs appeared to have a lower risk of adenomas, while among heavier individuals, minor allele carriers appeared to have an increased risk of adenomas. There was a statistically significant interaction between minor allele carrier status and BMI for three of the *TLR4* tagSNPs: rs10116253, rs1927911, and rs7873784. The influence of *TLR4* polymorphisms on colorectal adenomas has not been previously evaluated and future studies will likely need to examine specific subgroups in order to explicate the complex influences of *TLR4* SNPs.

Several aspects of our study merit discussion. The prospective design of our study allowed us to accurately characterize and properly pair cases and controls. Self-reported diagnoses of adenomas were confirmed and information on histology, size, location and total number of adenomas was collected from pathology reports. However, records were not obtained to confirm negative colorectal screening among controls, as done in some other cohort studies,[49,50] and thus some controls could have been misclassified. Our study was nested in an established epidemiologic cohort in which the fact of colonoscopy was ascertained between baseline and 2000 via questionnaires in 1996 and 2000. At that time, the heterogeneity of procedure completeness and quality was not recognized and therefore was not required for inclusion in the study. Although all participants received colonoscopies from either the local medical center or the local outpatient endoscopy center, we did not have information on center endoscopy performance characteristics. If participants received poor quality or incomplete colonoscopies, it is possible that adenomas were not detected, potentially misclassifying controls and/or the number of adenomas among cases. We expect that this misclassification would have likely biased our findings towards the null. Moreover, although participants did not report whether they received a screening or surveillance colonoscopy, cases were restricted to those with an incident polyp diagnosis, which should thus exclude individuals receiving surveillance colonoscopies. Participants with a history of inflammatory bowel disease were also excluded but information for hereditary genetic disorders (eg, familial adenomatous polyposis) was not collected. However, we do not expect this population-based cohort to be enriched with individuals with these inherited disorders. Additionally, our study participants were all Caucasian; patterns of association should be studied among other race/ethnicities.

We examined the association between adenoma risk and the same set of polymorphisms as our prior nested case-control study assessing colorectal cancer. Evaluating these associations among individuals of the same cohort provided the opportunity to directly compare the influence of genetics in two distinct stages of carcinogenesis. Hence, these SNPs were selected to further investigate a part of the mechanism linking obesity and inflammation and colorectal carcinogenesis. Because our main analysis evaluated SNPs capturing the same underlying pathways, as opposed to an agnostic analysis, we did not perform adjustment for

multiple testing. However, using Bonferroni correction ($P = 0.001$), none of the findings would remain significant. In addition, given our sample size, some of our analyses may have been underpowered. Nonetheless, these findings are useful for both descriptive and hypothesis-generating purposes.

Understanding etiology at various points in the natural history of colorectal neoplasia can offer essential insight into the prevention and control of disease. In this study, we evaluated the association between polymorphisms in genes related to obesity and inflammation and adenoma risk and compared these with the observed associations between the same SNPs and colorectal cancer in the same cohort. These pathways should be further assessed in larger studies to obtain a better comprehension of the mechanisms linking obesity, inflammation, and colorectal carcinogenesis.

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**TABLE 1**

Characteristics of colorectal adenoma cases and matched controls in the CLUE II cohort of Washington County, MD 1989

| **Characteristic** | **Cases (*n* = 135)** | **Controls (*n* = 269)** | ***P*[a]** |
|---|---|---|---|
| Age (year), mean (SD) | 55.3 (10.0) | 55.1 (10.0) | Matched |
| Female (%) | 48.9 | 49.1 | Matched |
| BMI (kg/m$^2$), mean (SD) | 26.4 (4.4) | 26.3 (3.9) | 0.92 |
| Family history of CRC (%) | 20.7 | 8.2 | <0.001 |
| Use of NSAIDs (%) | 31.1 | 30.1 | 0.82 |
| Use of diabetes medication (%) | 5.2 | 2.2 | 0.13 |
| Cigarette smoking status | | | |
| Never (%) | 41.5 | 55.0 | 0.01 |
| Former (%) | 42.2 | 33.1 | |
| Current (%) | 16.3 | 11.9 | |
| Ever use of female hormones (%)[b] | 37.9 | 48.5 | 0.12 |
| Daily intake, mean (SD)[c] | | | |
| Alcohol (g) | 6.9 (18.5) | 6.6 (16.4) | 0.90 |
| Folate (μg) | 400 (292) | 410 (253) | 0.51 |
| Red meat (g) | 76.7 (57.9) | 85.7 (64.7) | 0.20 |
| Energy (kcal) | 1,678 (614) | 1,754 (539) | 0.10 |
| Saturated fat (g) | 24.2 (10.9) | 25.5 (11.5) | 0.40 |
| Fiber (g) | 12.6 (5.7) | 13.2 (5.0) | 0.17 |
| Calcium (mg) | 837 (537) | 850 (435) | 0.35 |
| Adenoma case characteristics | | | |
| Histology[d] | | | |
| Tubular (%) | 76.3 | - | - |
| Villous/tubulovillous (%) | 37.8 | - | - |
| Location[d] | | | |
| Proximal colon (%) | 45.9 | - | - |
| Distal colon (%) | 55.6 | - | - |
| Rectum (%) | 20.7 | - | - |

| Characteristic | Cases (*n* = 135) | Controls (*n* = 269) | *P*[a] |
|---|---|---|---|
| ≥1 cm (%) | 20.7 | - | - |
| >1 adenoma (%) | 48.2 | - | - |

CRC, colorectal cancer; NSAIDs, non-steroidal anti-inflammatory drugs; SD, standard deviation.

Cases and controls matched on age, sex, race, and date of blood draw.

[a]From generalized estimating equations with exchangeable correlation structures and robust standard error estimations to account for the matched pair design of the study.

[b]Percentages based on female participants only.

[c]Percentages based on those who completed a valid food frequency questionnaire (107 cases and 184 matched controls).

[d]Percentages do not add up to 100% because individuals could contribute to more than one category.

## TABLE 2

Odds ratios and 95% confidence intervals of colorectal adenomas for 17 candidate single nucleotide polymorphisms in genes related to inflammatory response and obesity among cases and controls in the CLUE II cohort of Washington County, MD 1989

| Genotype | Cases, *n* | Controls, *n* | OR (95%CI)[a] |
|---|---|---|---|
| *IL10* | | | |
| rs1800896 | | | |
| A/A | 39 | 75 | 1.00 (Ref) |
| A/G | 63 | 127 | 0.94 (0.59–1.52) |
| G/G | 32 | 61 | 1.01 (0.58–1.77) |
| $p_{trend}$[b] | | | 0.98 |
| G-carrier | 95 | 188 | 0.97 (0.62–1.51) |
| rs1800872 | | | |
| C/C | 80 | 147 | 1.00 (Ref) |
| A/C | 46 | 76 | 1.12 (0.71–1.78) |
| A/A | 6 | 23 | 0.42 (0.15–1.16) |
| $p_{trend}$[b] | | | 0.38 |
| A-carrier | 52 | 99 | 0.97 (0.62–1.50) |
| *CRP* | | | |
| rs1800947 | | | |
| G/G | 115 | 239 | 1.00 (Ref) |
| C/G | 16 | 22 | 1.57 (0.79–3.13) |
| C/C | 2 | 1 | 4.36 (0.93–48.45) |
| $p_{trend}$[b] | | | 0.09 |
| C-carrier | 18 | 23 | 1.68 (0.86–3.28) |
| rs1205 | | | |
| C/C | 52 | 131 | 1.00 (Ref) |
| C/T | 60 | 95 | 1.65 (1.03–2.65) |
| T/T | 19 | 30 | 1.72 (0.87–3.38) |
| $p_{trend}$[b] | | | 0.04 |
| T-carrier | 79 | 125 | 1.67 (1.07–2.60) |
| *TLR4* | | | |
| rs4986790 | | | |
| A/A | 119 | 228 | 1.00 (Ref) |
| G-carrier[c] | 14 | 32 | 0.83 (0.43–1.57) |
| rs11536889 | | | |
| G/G | 94 | 191 | 1.00 (Ref) |
| C/G | 36 | 66 | 1.11 (0.70–1.78) |
| C/C | 4 | 4 | 2.06 (0.51–8.26) |
| $p_{trend}$[b] | | | 0.38 |

| Genotype | Cases, *n* | Controls, *n* | OR (95%CI)[a] |
|---|---|---|---|
| C-carrier | 40 | 70 | 1.17 (0.74–1.84) |
| *IL6* | | | |
| rs1800797 | | | |
| G/G | 46 | 79 | 1.00 (Ref) |
| A/G | 71 | 123 | 0.96 (0.61–1.51) |
| A/A | 17 | 52 | 0.53 (0.27–1.05) |
| $p_{trend}$[b] | | | 0.12 |
| A-carrier | 88 | 175 | 0.85 (0.55–1.31) |
| rs1800796 | | | |
| G/G | 118 | 229 | 1.00 (Ref) |
| C-carrier[c] | 13 | 15 | 1.63 (0.75–3.58) |
| rs1800795 | | | |
| G/G | 43 | 68 | 1.00 (Ref) |
| C/G | 68 | 126 | 0.86 (0.54–1.38) |
| C/C | 21 | 47 | 0.74 (0.38–1.44) |
| $p_{trend}$[b] | | | 0.36 |
| C-carrier | 89 | 173 | 0.84 (0.53–1.32) |
| *IL1B* | | | |
| rs1143627 | | | |
| T/T | 57 | 119 | 1.00 (Ref) |
| C/T | 59 | 102 | 1.26 (0.80–1.97) |
| C/C | 17 | 35 | 1.02 (0.54–1.94) |
| $p_{trend}$[b] | | | 0.65 |
| C-carrier | 76 | 137 | 1.19 (0.78–1.81) |
| *IL8* | | | |
| rs4073 | | | |
| T/T | 47 | 88 | 1.00 (Ref) |
| A/T | 62 | 109 | 1.04 (0.64–1.69) |
| A/A | 24 | 52 | 0.84 (0.46–1.54) |
| $p_{trend}$[b] | | | 0.61 |
| A-carrier | 86 | 161 | 0.97 (0.61–1.54) |
| *TNF* | | | |
| rs1800629 | | | |
| G/G | 94 | 181 | 1.00 (Ref) |
| A/G | 35 | 68 | 1.00 (0.63–1.58) |
| A/A | 3 | 10 | 0.60 (0.16–2.20) |
| $p_{trend}$[b] | | | 0.65 |
| A-carrier | 38 | 78 | 0.95 (0.61–1.49) |
| *RNASEL* | | | |
| rs486907 | | | |

| Genotype | Cases, *n* | Controls, *n* | OR (95%CI)[a] |
|---|---|---|---|
| G/G | 62 | 102 | 1.00 (Ref) |
| A/G | 54 | 108 | 0.80 (0.51–1.26) |
| A/A | 15 | 35 | 0.71 (0.36–1.39) |
| $p_{trend}$[b] | | | 0.23 |
| A-carrier | 69 | 143 | 0.78 (0.51–1.18) |
| *PPARG* | | | |
| rs1801282 | | | |
| C/C | 100 | 180 | 1.00 (Ref) |
| C/G | 28 | 63 | 0.82 (0.50–1.35) |
| G/G | 4 | 7 | 1.08 (0.89–3.94) |
| $p_{trend}$[b] | | | 0.57 |
| G-carrier | 32 | 70 | 0.85 (0.54–1.35) |
| *TCF7L2* | | | |
| rs7903146 | | | |
| C/C | 63 | 115 | 1.00 (Ref) |
| C/T | 51 | 108 | 0.86 (0.54–1.36) |
| T/T | 15 | 23 | 1.16 (0.56–2.39) |
| $p_{trend}$[b] | | | 0.98 |
| T-carrier | 66 | 131 | 0.92 (0.59–1.41) |
| *ADIPOQ* | | | |
| rs1501299 | | | |
| C/C | 60 | 131 | 1.00 (Ref) |
| A/C | 66 | 95 | 1.58 (1.00–2.49) |
| A/A | 7 | 32 | 0.44 (0.18–1.08) |
| $p_{trend}$[b] | | | 0.87 |
| A-carrier | 73 | 127 | 1.28 (0.83–1.96) |
| *LEP* | | | |
| rs2167270 | | | |
| G/G | 50 | 111 | 1.00 (Ref) |
| A/G | 71 | 119 | 1.39 (0.88–2.20) |
| A/A | 13 | 29 | 1.04 (0.48–2.24) |
| $p_{trend}$[b] | | | 0.44 |
| A-carrier | 84 | 148 | 1.33 (0.85–2.06) |

[a] From a conditional logistic regression model where cases and controls were matched on age, sex, race, and date of blood draw.

[b] Tests for trend evaluated by entering into the model an ordinal variable representing the number of minor alleles.

[c] ORs for minor homozygotes not estimable because of zero counts in cases or controls.

## TABLE 3

Odds ratios and 95% confidence intervals of colorectal adenomas for 19 tag single nucleotide polymorphisms in genes related to inflammatory response and obesity among cases and controls in the CLUE II cohort of Washington County, MD 1989

| Genotype | Cases, *n* | Controls, *n* | OR (95%CI)[a] |
|---|---|---|---|
| *IL10* | | | |
| rs1800890 | | | |
| A/A | 49 | 92 | 1.00 (Ref) |
| A/T | 58 | 104 | 1.03 (0.65–1.62) |
| T/T | 20 | 30 | 1.22 (0.63–2.33) |
| $p_{trend}$[b] | | | 0.61 |
| T-carrier | 78 | 134 | 1.07 (0.70–1.64) |
| rs1800894 | | | |
| C/C | 123 | 211 | 1.00 (Ref) |
| T-carrier[c] | 8 | 29 | 0.49 (0.22–1.12) |
| rs3021094 | | | |
| A/A | 117 | 209 | 1.00 (Ref) |
| A/C | 11 | 34 | 0.59 (0.29–1.20) |
| C/C | 2 | 2 | 1.59 (0.22–11.53) |
| $p_{trend}$[b] | | | 0.32 |
| C-carrier | 13 | 36 | 0.65 (0.34–1.27) |
| rs1554286 | | | |
| C/C | 95 | 158 | 1.00 (Ref) |
| C/T | 35 | 78 | 0.75 (0.46–1.23) |
| T/T | 3 | 13 | 0.39 (0.11–1.46) |
| $p_{trend}$[b] | | | 0.09 |
| T-carrier | 38 | 91 | 0.70 (0.44–1.12) |
| rs3024509 | | | |
| C/C | 120 | 215 | 1.00 (Ref) |
| T-carrier[c] | 13 | 38 | 0.65 (0.34–1.27) |
| rs3024496 | | | |
| C/C | 38 | 64 | 1.00 (Ref) |
| C/T | 62 | 122 | 0.85 (0.52–1.39) |
| T/T | 31 | 61 | 0.88 (0.50–1.54) |
| $p_{trend}$[b] | | | 0.63 |
| T-carrier | 93 | 183 | 0.86 (0.54–1.35) |
| rs3024498 | | | |
| A/A | 72 | 130 | 1.00 (Ref) |
| A/G | 53 | 101 | 0.92 (0.60–1.41) |
| G/G | 7 | 16 | 0.77 (0.31–1.90) |

| Genotype | Cases, *n* | Controls, *n* | OR (95%CI)[a] |
|---|---|---|---|
| $p_{trend}$[b] | | | 0.53 |
| G-carrier | 60 | 117 | 0.90 (0.59–1.35) |
| CRP | | | |
| rs2794521 | | | |
| T/T | 61 | 119 | 1.00 (Ref) |
| C/T | 57 | 92 | 1.19 (.77–1.82) |
| C/C | 10 | 25 | 0.73 (0.33–1.61) |
| $p_{trend}$[b] | | | 0.91 |
| C-carrier | 67 | 117 | 1.09 (0.73–1.64) |
| rs1417938 | | | |
| T/T | 66 | 127 | 1.00 (Ref) |
| A/T | 57 | 83 | 1.33 (0.85–2.09) |
| A/A | 6 | 24 | 0.47 (0.18–1.22) |
| $p_{trend}$[b] | | | 0.74 |
| A-carrier | 63 | 107 | 1.12 (0.74–1.72) |
| rs2808630 | | | |
| T/T | 62 | 120 | 1.00 (Ref) |
| C/T | 57 | 96 | 1.15 (0.75–1.76) |
| C/C | 10 | 26 | 0.69 (0.32–1.52) |
| $p_{trend}$[b] | | | 0.77 |
| C-carrier | 67 | 122 | 1.05 (0.70–1.58) |
| rs3093077 | | | |
| A/A | 121 | 220 | 1.00 (Ref) |
| C-carrier[c] | 11 | 31 | 0.61 (0.28–1.30) |
| *TLR4* | | | |
| rs2737190 | | | |
| A/A | 57 | 98 | 1.00 (Ref) |
| A/G | 56 | 94 | 1.00 (0.64–1.58) |
| G/G | 12 | 30 | 0.70 (0.33–1.49) |
| $p_{trend}$[b] | | | 0.50 |
| G-carrier | 68 | 124 | 0.94 (0.61–1.46) |
| rs10116253 | | | |
| T/T | 66 | 119 | 1.00 (Ref) |
| C/T | 47 | 74 | 1.13 (0.71–1.81) |
| C/C | 5 | 17 | 0.52 (0.18–1.54) |
| $p_{trend}$[b] | | | 0.70 |
| C-carrier | 52 | 91 | 1.05 (0.66–1.66) |
| rs1927914 | | | |
| A/A | 57 | 108 | 1.00 (Ref) |

| Genotype | Cases, *n* | Controls, *n* | OR (95%CI)[a] |
|---|---|---|---|
| A/G | 60 | 100 | 1.12 (0.72–1.74) |
| G/G | 13 | 35 | 0.69 (0.33–1.43) |
| $p_{trend}$[b] | | | 0.62 |
| G-carrier | 73 | 135 | 1.02 (0.67–1.56) |
| rs1927911 | | | |
| G/G | 79 | 139 | 1.00 (Ref) |
| A/G | 49 | 93 | 0.92 (0.59–1.43) |
| A/A | 6 | 23 | 0.45 (0.17–1.19) |
| $p_{trend}$[b] | | | 0.20 |
| A-carrier | 55 | 116 | 0.85 (0.55–1.30) |
| rs2149356 | | | |
| G/G | 54 | 81 | 1.00 (Ref) |
| G/T | 45 | 67 | 0.98 (0.58–1.63) |
| T/T | 9 | 26 | 0.51 (0.21–1.25) |
| $p_{trend}$[b] | | | 0.26 |
| T-carrier | 54 | 93 | 0.88 (0.54–1.45) |
| rs7873784 | | | |
| G/G | 86 | 155 | 1.00 (Ref) |
| C/G | 31 | 54 | 0.99 (0.58–1.68) |
| C/C | 1 | 6 | 0.33 (0.04–2.80) |
| $p_{trend}$[b] | | | 0.60 |
| C-carrier | 32 | 60 | 0.94 (0.55–1.60) |
| rs11536891 | | | |
| T/T | 94 | 168 | 1.00 (Ref) |
| C/T | 32 | 60 | 0.94 (0.57–1.55) |
| C/C | 1 | 7 | 0.28 (0.03–2.28) |
| $p_{trend}$[b] | | | 0.42 |
| C-carrier | 33 | 67 | 0.89 (0.54–1.47) |
| rs11536898 | | | |
| C/C | 90 | 148 | 1.00 (Ref) |
| A-carrier[c] | 20 | 43 | 0.76 (0.41–1.39) |

[a] From a conditional logistic regression model where cases and controls were matched on age, sex, race, and date of blood draw.

[b] Tests for trend evaluated by entering into the model an ordinal variable representing the number of minor alleles.

[c] ORs for minor homozygotes not estimable because of zero counts in cases or controls.