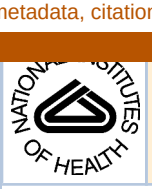

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Moderate Alcohol Consumption is Protective Against Colorectal Adenomas in Smokers

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Abstract

Background—Although some studies have shown an association between alcohol consumption and colorectal adenomas, the effect of moderate alcohol consumption is not well-defined, nor is the interaction between alcohol and smoking.

Aim—To investigate the relationship between different levels of alcohol consumption and colorectal adenomas and to determine whether smoking modifies this relationship.

Methods—Eligible patients who underwent a complete colonoscopy were included (179 cases and 466 controls). Alcohol consumption was obtained from a lifestyle questionnaire. Patients were divided into three groups: 1) Abstainers: 0 drinks/week; 2) Moderate drinkers: >0-<7 drinks/week; 3) Heavy drinkers: >=7 drinks/week. Odds ratios (OR) were calculated using logistic regression, controlling for gender, age, body mass index, use of non-steroidal anti-inflammatory medications. Results were stratified by the number of years smoked.

Results—The proportion of patients with adenomas was 29.6% in abstainers, 22.1% in moderate drinkers, and 36.7% in heavy drinkers. There was significant modification of the relationship between alcohol consumption and colorectal adenomas by smoking. For individuals who had never smoked, heavy drinkers were at significantly increased odds of having an adenoma compared to moderate drinkers (OR 3.08; 95% CI: 1.50-6.32), while no difference was seen for abstainers (OR 0.99; 95% CI: 0.52-1.89). Similarly, among individuals who had smoked 1-14 years, heavy drinkers were at increased odds of having an adenoma compared to moderate drinkers (OR 2.61; 95% CI: 1.04-6.51), and no difference was seen for abstainers (OR 1.02; 95% CI: 0.33-3.10). Somewhat unexpectedly, among individuals who had smoked for 15 or more years, abstainers were at increased odds of having an adenoma compared to moderate drinkers (OR 2.04; 95% CI: 0.91-4.59), while heavy drinkers were not at increased odds of having an adenoma (OR 0.73; 95% CI: 0.27-1.97).

Conclusions—Consumption of less than seven alcohol drinks per week does not increase the risk of having a colorectal adenoma. We found evidence in this study that moderate alcohol consumption among long-term smokers may potentially decrease the risk of an adenoma compared to abstainers.

Introduction

The role of alcohol consumption and colorectal neoplasia has been widely investigated, yet the exact relationship remains elusive. Interpretation of the data regarding the relationship between alcohol consumption and colorectal cancers and adenomas is hindered by the varying studying designs, outcome measures, cutoff values for categories of drinkers of alcohol, and findings

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that are specific for certain subgroups. For colorectal cancer, some studies suggest an increase risk in only colon (1) or only rectal cancer (2-4), while others make no distinction and report an increase in the risk of colorectal cancer (5,6). Some studies have implicated beer (3,4,6,7) or liquor (4-6) consumption (compared to wine) as the primary beverages associated with the increased risk of cancer, though sometimes the total alcohol consumption is not associated with an increased risk of colorectal cancer.

Because colorectal cancer may take several decades to develop from the time of the initiating event, there has been interest in studying risk factors related to colorectal adenomas, the precursors of most cases of colorectal cancer. The evidence for a role of alcohol consumption in colorectal adenomas is also equivocal. Several studies indicate that increasing alcohol consumption is associated with an increased risk of having an adenoma (8-13). However, there are several studies that have failed to find a significant association between alcohol consumption and colorectal adenomas after adjusting for potential confounders, including smoking. Only a few studies have looked at the joint effects of smoking and alcohol consumption on the risk of colorectal adenomas, with a suggestion that when both are present, there is an additive effect of increasing the risk for an adenoma (12,13).

The purpose of this study was to assess the relationship between alcohol consumption and the risk of having a colorectal adenoma using data from a study of risk factors for colorectal adenomas during which extensive dietary and lifestyle variables were assessed. Specifically, we investigated whether the relationship between alcohol consumption and colorectal adenomas was linear or whether a threshold level of alcohol consumption must be exceeded before the odds of having an adenoma increase. Finally, this study also investigated whether the relationship between alcohol consumption and colorectal adenomas was modified by smoking.

Methods

Study Population

The Diet and Health Study 4 is a case-control study of outpatients who underwent colonoscopy for a variety of indications, including colorectal cancer screening, between November 2001 and December 2002 at the University of North Carolina hospitals (Chapel Hill, NC). Eligible participants were enrolled if they gave informed consent and agreed to participate in a telephone interview. All subjects were between 30 and 80 years old and both men and women were eligible to participate. Exclusion criteria included a personal history of colon cancer (or adenoma), inflammatory bowel disease, or history of previous colon resection. Patients were also excluded if they were unable to give informed consent, had a polyposis (>100 polyps) syndrome, or had an incomplete examination (cecum not reached). Cases were defined as participants who had one or more adenomatous polyps. Control subjects had no adenomatous polyps. The institutional review board at the University of North Carolina School of Medicine approved this study. A total of 645 subjects were enrolled as part of DHS 4, with 179 cases and 466 controls.

Data Collection

Weight and height were recorded at the time of colonoscopy and were used to calculate body mass index (BMI). Participants were contacted by telephone within 12 weeks of their colonoscopy for assessment of dietary and lifestyle variables by a trained interviewer. A lifestyle questionnaire was used to collect information about demographics, personal and family medical history, physical activity, smoking history (recorded as number of years smoked), and utilization of certain medications, including non-steroidal anti-inflammatory medications (NSAID's). Dietary data was also collected using a food frequency questionnaire

(FFQ) developed by the National Cancer Institute (NCI). This FFQ is a validated dietary assessment that provides reasonable nutrient estimates (14,15). Alcohol consumption was recorded as part of the lifestyle questionnaire. To investigate whether the relationship between colorectal adenomas and alcohol consumption was linear, participants were divided into one of three categories based on their level of alcohol consumption: 1) abstainers (0 drinks/week, n=199); 2) moderate drinkers (>0 - <7 drinks/week, n=299); and 3) heavy drinkers (>=7 drinks/week, n=147).

Statistical Analyses

The Student's t-test and the chi-square test were performed for the statistical comparison of means and proportions between groups, respectively. Gender, race, age, smoking history, BMI, total energy consumption, daily fiber intake, and NSAID use were analyzed in simple bivariate analyses to identify potential confounders. Multivariate analyses were performed using logistic regression to assess the relationship between the level of alcohol consumption and the presence of an adenoma on colonoscopy, while adjusting for covariates age, gender, BMI, NSAID use, and smoking. Interaction terms were initially included in the logistic regression model to assess for effect modification of the relationship between alcohol consumption and colorectal adenomas. Because an interaction between smoking and alcohol consumption was discovered, smoking was categorized into three groups based on the number of years smoked: 1) never smoked (n=332); 2) smoked 1-14 years (n=141; and 3) smoked 15 or more years (n=172). Appropriate dummy variables for categories of alcohol consumption and smoking history were used during multivariate analysis. All data were entered into and analyzed using Stata 8.2 statistical software (STATA Corp., College Station, TX). A p-value of less than 0.05 was considered significant for all situations.

Results

As shown in Table 1, the average age and racial distribution were similar in the cases and the controls. However, there were significant differences in many other baseline characteristics. Men represented 59% of the cases compared to 39% of the controls ($p<0.001$). Cases had a higher average BMI ($p=0.015$) and had significantly more smoking exposure ($p=0.047$) compared to controls. There was no significant difference between cases and controls regarding regular use of NSAID's over the past 5 years.

Cases (8.6 ± 2.3 drinks/week) consumed twice as many alcoholic beverages compared to controls (4.2 ± 0.3) in an unadjusted analysis ($p=0.004$). Heavy drinkers were the most likely to have an adenoma (36.1%); abstainers were the next most likely to have an adenoma (29.6%); and moderate drinkers were the least likely to have an adenoma (22.1%). In unadjusted analyses, alcohol abstainers were more likely to have had an adenoma on colonoscopy compared to moderate drinkers (OR 1.49; 95% CI: 0.99-2.24). Heavy drinkers had an increased risk of having an adenoma on colonoscopy (OR 2.05: 95% CI 1.33-3.16) compared to moderate drinkers. Because of the potential confounding between alcohol consumption and other demographic, dietary, and lifestyle risk factors, the relationship between potential confounders and alcohol consumption was also analyzed.

Several differences were seen between the three categories of alcohol consumers with respect to other exposures that could impact adenoma risk. As shown in Table 2, both abstainers (10.8 years ± 0.9) and heavy drinkers (9.7 years ± 1.1) had smoked for a greater number of years (overall $p=0.01$) compared to moderate drinkers (7.3 years ± 0.8). Similarly, both abstainers (58.2 years ± 0.7) and heavy drinkers (57.2 years ± 0.8) were significantly older (overall $p<0.001$) compared to moderate drinkers (54.6 years ± 0.6). While the vast majority of participants in this study were white, abstainers were much more likely to be non-white (predominantly African-American) compared to the other two groups ($p<0.001$). Abstainers

($28.7\ kg/m^2 \pm 0.4$) also had a significantly higher mean BMI (overall $p<0.001$) compared to both moderate drinkers ($27.2\ kg/m^2 \pm 0.3$) and heavy drinkers ($25.7\ kg/m^2 \pm 0.5$). Almost two of every three individuals who consumed more than 7 alcoholic drinks per week were male, which was significantly different compared to the other two groups, where the majority of participants were female (overall $p<0.001$). There was no significant difference between the three groups regarding the proportion of individuals who had regularly used NSAID's over the past 5 years. Heavy drinkers consumed significantly more calories per day (overall $p<0.001$) compared to abstainers and moderate drinkers. Heavy drinkers consumed 22.3 (± 0.8) grams of fiber a day, which was statistically significantly more compared to abstainers ($p=0.02$) but similar compared to moderate drinkers.

Multivariate analysis

To more accurately assess the relationship between alcohol consumption and colorectal adenomas, we controlled for the number of years smoked, age, gender, BMI, and NSAID use. Interaction terms (for alcohol and the covariates) were evaluated as well. The interaction variable for smoking and alcohol was significant ($p=0.023$), while all other interaction terms were non-significant and were dropped from all future analyses. Including the interaction term for smoking and alcohol, the number of years smoked was associated with a significant increase in the odds of having an adenoma on colonoscopy (OR of 1.35 for each 10 years of smoking; 95% CI: 1.03-1.76).

Because of the effect modification by smoking, it was necessary to stratify the results for the relationship between alcohol consumption and adenomas by level of smoking history. The relationship between alcohol consumption and colorectal adenomas was analyzed separately for the three groups of smokers (adjusted for age, gender, BMI, and NSAID use). As shown in Figure 1, for individuals who had never smoked, heavy drinkers had increased odds of having an adenoma compared to abstainers (adjusted OR 3.08; 95% CI: 1.50-6.32) and moderate drinkers (adjusted OR 3.11; 95% CI: 1.40-6.92). The odds of having an adenoma for moderate drinkers were almost identical to the odds for abstainers (adjusted OR 1.01; 95% CI: 0.53-1.92) among individuals who had never smoked. Among individuals who had smoked one to fourteen years, the results were quite similar to that seen among those who had never smoked. Heavy drinkers had increased odds of having an adenoma compared to abstainers (adjusted OR 2.56; 95% CI: 0.81-8.11) and moderate drinkers (adjusted OR 2.61; 95% CI: 1.04-6.51). As was the case for never smokers, the odds of having an adenoma for moderate drinkers was quite similar to the odds for abstainers (adjusted OR 0.98; 95% CI: 0.32-3.00) for individuals who had smoked one to fourteen years.

For individuals who had smoked at least 15 years, the association between alcohol consumption and colorectal adenomas was significantly different than for the group that had never smoked and the group that had smoked for one to fourteen years. In this group of smokers, abstainers from alcohol were more likely to have had an adenoma compared to moderate drinkers (adjusted OR 2.04; 95% CI: 0.91-4.59). Heavy drinkers were not more likely to have had an adenoma compared to moderate drinkers (OR 0.73; 95% CI: 0.27-1.97), among individuals who had smoked for fifteen or more years.

When the group consuming 7 or more drinks/week was subdivided into two groups (one that consumed 7-<14 drinks per week and another group that consumed 14 or more drinks per week), a dose-response relationship emerged. However, because of a lack of statistical power, significant differences were only seen among non-smokers. Among those who had never smoked, the OR for having an adenoma in individuals who consumed 7-<14 drinks was 2.73 (95% CI: 1.14-6.49) compared to moderate drinkers. For the group that consumed 14 or more drinks, the OR for having an adenoma was 3.63 (95% CI: 1.37-9.59) compared to moderate drinkers. Among those who had smoked 1-14 years, those who drank 7-<14 drinks/week had

an OR of 2.27 (95% CI: 0.80-6.46) for having an adenoma compared to moderate drinkers, while those who consumed 14 or more drinks had OR of 3.38 (95% CI: 0.92-12.34). Interestingly, for those who had smoked for 15 or more years, both the group that consumed 7-< 14 drinks/week (OR 0.27, 95% CI: 0.07-0.99) and the group that consumed 14 or more drinks/week (OR 0.48, 95% CI: 0.14-1.69) were at decreased odds for having an adenoma compared to abstainers, though the latter was not statistically significant. No significant changes in the results were seen when the group of moderate drinkers was divided into two groups, one that consumed less than two drinks per week and one that consumed two or more alcoholic drinks per week.

Discussion

The purpose of this study was to assess the associations of different levels of alcohol consumption and the odds of having a colorectal adenoma on colonoscopy. Several interesting findings are evident from this study. There were distinct differences regarding the dietary, demographic, and lifestyle characteristics that characterized the alcohol abstainers, moderate drinkers, and heavy drinkers in this study. Abstainers from alcohol were the oldest group, had the highest BMI, and had the highest proportion of non-whites. Interestingly, abstainers also had the highest mean number of years smoked, which may reflect some distinct cultural pattern of this group. Although it is likely that some of this increase in mean number of years smoked among alcohol abstainers is due to the fact that they were somewhat older than the other groups, it is not the full explanation since the difference in ages compared to the other two groups is essentially the same as the difference in mean number of years smoked, and over half of abstainers had never smoked.

The major finding of this study demonstrates that moderate alcohol consumption (less than seven drinks per week) does not appear to increase the risk of having a colorectal adenoma, and may offer some protection. In unadjusted analysis, abstainers had 1.49 times the odds of having an adenoma compared to moderate drinkers. Following adjustment for the appropriate confounders and effect modifiers (smoking), the odds of having an adenoma were essentially the same for abstainers compared to moderate drinkers, expect for those who had smoked for at least 15 years. The interesting finding in our study was that there was not a synergistic or additive effect of heavy alcohol consumption and heavier smoking exposure. In fact, in the subjects who had smoked 15 years or more, abstainers were much more likely to have had an adenoma compared to moderate and heavy drinkers.

There has been a vigorous investigation into the association of alcohol consumption and the risk of colorectal adenomas and cancer. Our study demonstrates that the probability of an adenoma increases when 7 or more drinks of alcohol are consumed per week for those who had smoked for less than 15 years, and that the odds in this group are increased even further for those who consumed 14 or more drinks compared to those who consumed between seven and fourteen alcoholic drinks per week. These findings provide evidence for both a threshold level above which the risk of an adenoma increases as well evidence for a dose-response relationship that occurs when this threshold level of alcohol consumption is exceeded.

Previous literature regarding the association between alcohol consumption and colorectal adenomas has been inconsistent. Anderson *et al* recently reported that heavy drinkers (>=8 drinks/week) of beer and liquor had an increased risk of colorectal neoplasia (8), but found that consumption of one to eight glasses of wine per week was protective. They controlled for smoking in multivariate logistic regression analysis but did not report results for the possible interaction between smoking and alcohol consumption. While Lieberman *et al* showed an increased risk of adenoma with current smoking and current moderate-heavy alcohol consumption (10), Breuer-Katschinski *et al* found no such association and concluded that

neither smoking nor alcohol consumption played a major role in the formation or growth of colorectal adenomas (16). Other studies have reported intermediate results. Erhardt *et al* found that smoking but not alcohol was a significant risk factor for colorectal adenomas (17). Similarly, in a study by Nagata *et al*, only smoking for more than 30 years was associated with an increased adenoma risk and no association was seen for alcohol consumption (18). Gondal *et al* found smoking to be associated with adenomas in both men and women, while alcohol was only associated with adenomas in men (9). Longnecker *et al* reported current (but not remote) smoking was associated with an increased risk of adenomas, but that heavy alcohol consumption was only associated with a non-significant increase in adenoma risk (19). In a trial of recurrent adenoma prevention, Baron *et al* also found no association with smoking but did find that individuals who consumed seven or more drinks per week were at an increased risk for having a recurrent adenoma (11). In our study, failure to include an interaction term for the joint effect of alcohol and smoking would have obscured the increased risk of an adenoma with increasing number of years smoked. Since many of the studies that have assessed the association between alcohol and colorectal adenomas have also evaluated the independent effect of smoking, failure to assess the joint effects of both exposures may have lead some authors to conclude that there was not an association between alcohol, smoking, and colorectal adenomas.

Because of the inconclusive nature of the existing evidence regarding whether there is a true association between alcohol consumption and colorectal adenomas, we investigated many other dietary variables (not presented in the results section) in an attempt to identify other potential confounders. For example, we investigated whether total energy consumption or fiber intake should be adjusted for in assessing the relationship between alcohol consumption and colorectal adenomas because there is evidence for a role of one or both factors (20-22). Although total energy consumption was significantly different amongst abstainers, moderate drinkers, and heavy drinkers, it was not significantly different between cases and controls and adjusting for total energy consumption in the logistic regression model did not appreciably alter the odds ratios for the alcohol groups. Similarly, fiber intake was modestly different between the three alcohol groups, it but was almost identical in cases compared to controls and its inclusion into the multivariate logistic regression model also did not significantly alter the odds ratios for the alcohol groups. Additionally, although there is evidence in the literature supporting a possible protective role against colorectal neoplasm for certain micronutrients (23-27), we found no significant differences between cases and controls regarding selenium, zinc, folate, and calcium intake , nor did we find any differences in the intake of these micronutrients between the groups of alcohol consumers.

A few studies have reported on the potential interaction between alcohol consumption and smoking on the risk of having an adenoma of the colon or rectum. Martinez *et al* found that smoking (current and former) and increasing alcohol consumption increased odds of having an adenoma (12). When analyzing their subjects as drinkers or non-drinkers, they found an additive joint effect of smoking and alcohol on the risk of having an adenoma (greater amongst current smokers). Interestingly, when controlling for smoking, the authors found that individuals consuming 2.31-9.46 grams of alcohol per day had the highest risk of having an adenoma, higher than those consuming 9.47-67.36 grams of alcohol per day. Takeshita *et al* demonstrated a positive synergistic increase in adenoma risk when both smoking and alcohol are present as risk factors (13).

If alcohol or smoking play a role in the development of adenomas, the mechanism is not known. There is some suggestion for the role of folate (24,28,29). Additionally, both smoking and alcohol have been associated with expression of the tumor suppressor gene p53. Terry *et al* demonstrated that alcohol intake was associated with p53 over-expression while smoking may be inversely related to p53 expression (30). In our study, the finding of decreased odds of

having an adenoma with increased alcohol consumption among those who had smoked for 15 years or more could be related to the independent effects of both agents on the various oncogenes or tumor suppressors that play a role in colorectal carcinogenesis. Conversely, the finding may be the result of a separate dietary or lifestyle variable that influences the development of colorectal adenomas and has some unusual distribution across the various alcohol and smoking groups. Finally, this finding may also represent a chance occurrence and that no such relationship truly exists.

In summary, the results of this study indicate that moderate alcohol consumption does not increase the odds of having an adenoma and may even have a protective effect, especially among those with greater smoking exposure histories. For those individuals with little or no smoking history, a threshold level of seven or more alcohol drinks per week was associated with an increased risk of having an adenoma, and this risk was further increased in the subset of participants who consumed fourteen or more drinks per week. The mechanisms by which alcohol and smoking influence the development of colorectal neoplasms individually as well as in combination is poorly understood.

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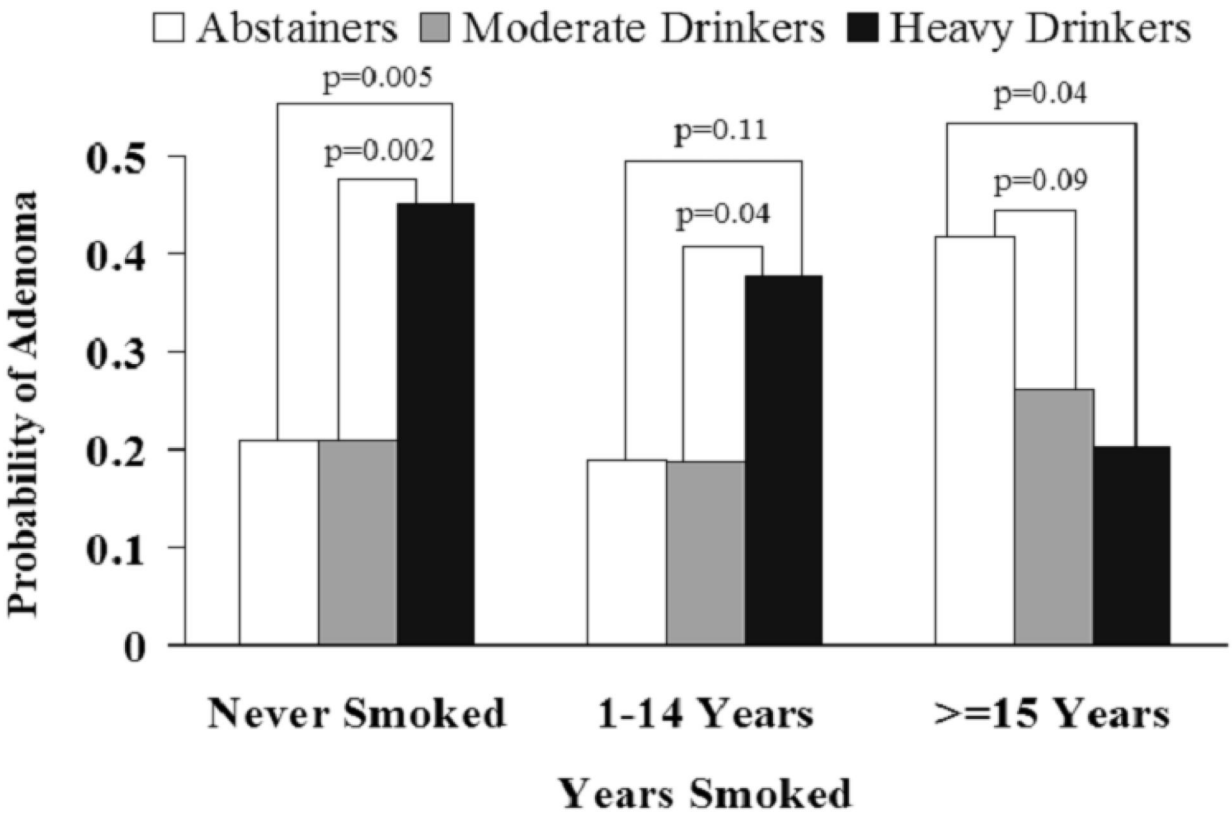

Figure 1.
Effect of number of years smoked on the relationship between alcohol consumption and the odds of having an adenoma.

Table 1

Demographics and lifestyle variables by case-control status.

Characteristic	Controls (n=502)	Cases (n=203)	p-value
Age (y)	55.8 ± 0.5	57.1 ± 0.7	0.134
Sex (%Male)	39.1%	59.1%	<0.001
Race (%White)	79.0%	81.2%	0.507
BMI (kg/m^2)	27.1 ± 0.3	28.3 ± 0.4	0.015
Years Smoked	8.3 ± 0.6	10.8 ± 1.1	0.047
Regular NSAID use past 5 years	53.2%	49.7%	0.417
Energy Consumption (kcal/day)	1948 ± 42	2068 ± 77	0.145
Daily fiber intake (g)	20.9 ± 0.4	20.7 ± 0.7	0.828

Table 2

Characteristics of confounders by level of weekly alcohol consumption.

	Non-drinkers	0-<7 Drinks/week	>=7 drinks/week	P-value
Years Smoked	10.8 ± 0.9	7.3 ± 0.8	9.7 ± 1.1	0.0106
Age (y)	58.2 ± 0.7	54.6 ± 0.6	57.2 ± 0.8	0.0001
Race (% White)	66%	86%	93%	< 0.0001
BMI (kg/m^2)	28.7 ± 0.4	27.2 ± 0.3	25.7 ± 0.5	< 0.0001
Gender (%Male)	39%	38%	65%	< 0.0001
Regular NSAID use past 5 years	56%	48%	56%	0.1215
Energy Consumption (kcal/day)	1951 ± 66	1877 ± 54	2234 ± 77	0.0007
Daily Fiber Intake	20.0 ± 0.7	20.7 ± 0.5	22.3 ± 0.8	0.0713