Physical Activity and Reduced Risk of Incident Sporadic Colorectal Adenomas: Observational Support for Mechanisms Involving Energy Balance and Inflammation Modulation

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To investigate the role of physical activity, energy balance, and inflammation on the risk of incident sporadic colorectal adenoma, the authors conducted a community- and colonoscopy-based case-control study (n = 177 cases, n = 228 controls) in Winston-Salem and Charlotte, North Carolina, from 1995 to 1997. Participants reported energy intake by a semiquantitative food frequency questionnaire, daily physical activity levels by a standardized questionnaire, and anthropometrics by self-assessment. The odds ratios for adenomas comparing the highest and lowest quantiles of exposure were 0.63 (95% confidence interval (CI): 0.34, 1.17) for physical activity, 0.80 (95% CI: 0.37, 1.73) for total energy intake, 0.70 (95% CI: 0.37, 1.34) for body mass index, 1.46 (95% CI: 0.73, 2.92) for waist/hip ratio, and 2.40 (95% CI: 1.24, 4.63) for height. For the combined effects of these factors, risk was particularly low for those with higher physical activity and low waist/hip ratio (odds ratio = 0.37, 95% CI: 0.18, 0.75) or shorter stature (odds ratio = 0.32, 95% CI: 0.16, 0.62). The inverse effect of physical activity was apparent only among those not taking nonsteroidal antiinflammatory drugs (odds ratio = 0.49, 95% CI: 0.25, 0.94). These findings add further evidence that physical activity and overall patterns indicating positive energy balance increase the risk of adenoma. Furthermore, the results suggest indirectly that biologic mechanisms related to inflammation may play a role in the beneficial effect of physical activity on the risk of incident adenoma.

adenoma; anti-inflammatory agents, non-steroidal; body constitution; body height; body mass index; colorectal neoplasms; exertion

Abbreviations: CI, confidence interval; MET, metabolic equivalent; NSAID, nonsteroidal antiinflammatory drug.

In the United States, colorectal cancer is the third most common cancer in men and women, with 147,500 new cases expected in 2003 (1). Worldwide, incidence rates vary approximately 20-fold with developed countries having the highest rates (2). Migrants from low-incidence countries tend to acquire this cancer according to the rates of their adopted countries within the first generation in their new country (3, 4). These differences indicate the importance of
informed consent, were eligible to participate. Subjects were 
years, of either sex and any race, and capable of signing 
Winston-Salem and Charlotte, North Carolina, from April 
Markers for Adenomatous Polyps Study data. Participants in 
inally designed to assess risk biomarkers of colorectal 
community- and colonoscopy-based case-control study orig-
final sample included 405 participants (men: 
were successfully contacted. Of these, 420 (68 percent) 
cluded participants with hyperplastic and “other” 
national Polyp Study (26). Polyps were categorized as 
vided informed consent prior to colonoscopy. Fifteen 
were excluded because of missing data in the 
30–74) self-reported total energy intake. The 
questionnaires or implausibly low (<500 kcal/day) or 
cluded if they had previous adenomas or any of the 
the following conditions: familial adenomatous polyposis, 
Gardner’s syndrome, ulcerative colitis, Crohn’s disease, 
incident colorectal cancer, or prevalent cancer other than 
nonmelanoma skin cancer. Of 2,246 participants screened, 
percent of those eligible) were successfully contacted. Of these, 420 (68 percent) 
cluded before colonoscopy. Fifteen 
were incident sporadic adenoma cases (men: n = 107; 
polyps, as long as no adenomas were identified. Categorical 
shape, type, degree of dysplasia, or location. All participants 
neoplasm (21). Accordingly, we report herein the 
results of analyses of a case-control study of colorectal 
reduce risk of colorectal neoplasms through mechanisms 
involving energy balance and modulation of colonic inflammation.

MATERIALS AND METHODS

The Markers for Adenomatous Polyps Study was a 
community- and colonoscopy-based case-control study originally 
designed to assess risk biomarkers of colorectal adenomas. This article represents a secondary analysis of the 
Markers for Adenomatous Polyps Study data. Participants in the study were recruited upon referral for routine elective 
energy balance, such as total energy intake and body size 
characteristics, suggest that an effect of physical activity 
may occur through its role in overall energy balance (10–20). In addition, a recent study also suggested that increased 
physical activity may decrease proinflammatory prostaglandin E\(_2\) in the colorectal intestinal mucosa independently of body mass index, which was positively associated with 
prostaglandin E\(_2\) (21). Accordingly, we report herein the 
results of analyses of a case-control study of colorectal adenomas to investigate whether physical activity may 
reduce risk of colorectal neoplasms through mechanisms involving energy balance and modulation of colonic inflammation.

Colonoscopy and pathology

Colonoscopy of all participants was performed in the usual 
manner. All polyps were removed and placed in separate 
labeled containers. The location, shape, and in vitro greatest 
diameter of all polyps were recorded.

Pathology slides for polyp specimens were evaluated by a 
study index pathologist using standardized criteria from the 
National Polyp Study (26). Polyps were categorized as 
adenomas, hyperplastic polyps, or “other.” The characteristics of each adenoma were noted, including histologic type (villous, tubular, tubulovillous) and degree of dysplasia (mild, moderate, or severe).

Statistical analysis

Cases included all participants with one or more histologically 
confirmed adenomas, regardless of their number, 
shape, type, degree of dysplasia, or location. All participants who had no adenomas were included as controls. The control group included participants with hyperplastic and “other” polyps, as long as no adenomas were identified. Categorical 
variables for physical activity, total energy intake, and 
anthropometrics were used in all analyses. Values for moderate and vigorous activity (MET-hours per day) were 
combined to create the indicator of physical activity (moderate-vigorous physical activity). Cutpoints for quartiles of physical activity were based on the distribution 
among controls. Categorical variables for total energy intake and the anthropometrics were based on the sex-specific 
distributions among controls. Total energy intake was 
determined from the semiquantitative food frequency questionaire as the mean total daily caloric intake (kcal per day). Variables for height (m), body mass index (weight (kg)/height (m)^2 (kg/m^2)), waist circumference (cm), and waist/hip ratio (waist circumference/hip circumference) were

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developed from the self-reported measures of height, weight, waist circumference, and hip circumference. NSAID use was defined as a “yes/no” variable for use of nonaspirin NSAIDs.

Age- and sex-adjusted mean baseline characteristics for cases and controls were computed for continuous variables using analysis of covariance. Comparisons of categorical variables were performed using the chi-square test of proportions. The odds ratio with 95 percent confidence interval was calculated as a measure of association of incident sporadic adenoma with various risk factors using standard logistic regression methods for case-control studies. The criteria for inclusion of variables in the final models included biologic plausibility, fit at the ≤0.10 level of significance, and/or evidence of confounding as indicated by the variable’s effect on the association between the primary exposure variables and adenoma. The variables considered as potential covariates included age, sex, height, weight, pack-years of smoking (packs of cigarettes smoked per day times the number of years smoked), alcohol consumption per day (grams per day), history of a first-degree relative (mother/father, sister/brother, or daughter/son) with colorectal cancer, regular use of nonaspirin NSAIDs, regular use of aspirin, and weight loss of more than 10 pounds (4.54 kg) within 3 months. The dietary factors considered as potential confounders included the daily intake of fat, protein, carbohydrates, sucrose, fiber, fruits/vegetables, red meat, cholesterol, folate, calcium, and total vitamins C and D.

The variables retained as covariates in final logistic models were age, sex, history of a first-degree relative with colorectal cancer, pack-years of smoking, daily intakes of sucrose and calcium, and regular use of NSAIDs (excluding aspirin). Models for each of the primary exposure variables (categorical variables for moderate-vigorous physical activity, total energy intake, body mass index, waist/hip ratio, waist circumference, height, and NSAIDs) were evaluated and included the other primary exposure variables as covariates, except the model for waist circumference. Tests for trend were completed across tertiles and quartiles of the primary exposure variables using the mean value at each exposure level to scale the tests.

RESULTS

Cases tended to be older, men, smokers, and consumers of more alcohol relative to controls (table 1). On average, cases were less physically active and taller, had a higher waist/hip ratio, and consumed less total carbohydrates, sucrose, and calcium than did controls. A higher proportion of controls regularly used NSAIDs and had a first-degree relative with colorectal cancer.

The age-, sex-, and multivariate-adjusted associations for the primary exposure variables with risk of adenomas are presented in table 2. Higher levels of moderate-vigorous physical activity were associated with a 40–50 percent reduction in risk of adenomas, although the tests for trend were only of borderline statistical significance. A suggestion of a “U-shaped” association with body mass index, a direct association with waist/hip ratio and height, but no clear relation between total energy intake and adenoma risk were found. Taking NSAIDs regularly appeared to reduce adenoma risk by about 40 percent.

The multivariate-adjusted associations of the primary exposure variables according to NSAID use are presented in table 3. There was a halving of risk with high physical activity among those who did not regularly use NSAIDs, but no reduction in risk among NSAID users was found.

Table 4 presents the joint and combined effects of physical activity with waist/hip ratio and height on adenoma risk. Substantial reductions in adenoma risk were associated with increased levels of physical activity at each level of waist/hip ratio and height. The findings were statistically significant except for taller individuals. Additionally, compared with the referent category of high waist/hip ratio or height and low physical activity, those with a low waist/hip ratio or height who were also more physically active had the lowest risk of adenoma. Not surprisingly with our modest sample size, none of the multiplicative interaction terms were statistically significant in these logistic models.

The three-way joint and combined effects of physical activity, total energy intake, and waist/hip ratio or height are presented in table 5. Even though these data are sparse, there are patterns suggesting a reduced adenoma risk with higher levels of physical activity for each combination of total energy intake and waist/hip ratio, as well as three of the four combinations of total energy intake and height. The lowest adenoma risk was found among those with the highest physical activity who also had high total energy intake but a low waist/hip ratio or height.

The three-way joint and combined effects of physical activity, height, and waist/hip ratio are presented in table 6. Though data are sparse in this analysis, patterns suggesting decreased adenoma risk with higher levels of physical activity were noted for each combination of height and waist/hip ratio. The association with increased physical activity appears to be strongest among those who are shorter, with either a low or a high waist/hip ratio.

DISCUSSION

While adding to the already consistent findings in the literature that increased levels of moderate-vigorous physical activity reduce risk of incident sporadic adenoma, this study provides support for hypotheses that this reduction in risk may be, at least in part, through mechanisms involving energy balance and colonic inflammation modulation. We hypothesized that the antiinflammatory effect of NSAIDs on the colonic epithelium is so strong that the relative contribution by physical activity would be inconsequential, and thus a physical activity-adenoma association would not be detectable among NSAID users, yet would be quite strong among persons not taking NSAIDs. Our data strongly support this hypothesis and, thus, support hypotheses that physical activity may, through means as yet unknown, favorably modulate colonic inflammation, thus reducing risk of colorectal neoplasms. Physical activity as a main effect was associated with a nonstatistically significant approximate one-third reduction in risk, and two surrogate indicators of later and early life energy balance, waist/hip ratio and height, were associated with an approximate 1.5-fold increase in
risk (not statistically significant) and an approximate 2.5-fold (statistically significant) increase in risk, respectively. Notably, we consistently found statistically significant stronger inverse associations of physical activity with adenoma in persons with surrogate indicators of lifelong lower energy balance, such as a shorter stature and a lower waist/hip ratio, alone and (especially) in combination. Taken together, these findings support the hypothesis that physical activity, at least in part, may protect against colon cancer through its contribution to avoiding/reducing positive energy balance.

There was no clear evidence of an interaction of physical activity and body size characteristics with total energy intake, though low statistical power due to small sample

| TABLE 1. Selected characteristics of participants, Markers of Adenomatous Polyps Study, 1995–1997 |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Characteristics | Cases (n = 177)*,† | Controls (n = 228)*,† | p value‡ |
| Demographics | | | |
| Age (years) | 58.2 (0.7) | 56.1 (0.6) | 0.03 |
| Men (%) | 60 | 36 | 0.0001 |
| White (%) | 87 | 90 | 0.30 |
| Education: greater than high school (%) | 47 | 49 | 0.66 |
| Family history of colorectal cancer (%)§ | 20 | 36 | 0.001 |
| Alcohol use | | | |
| Ever used (%) | 77 | 63 | 0.002 |
| Daily use (g/day) | 7.1 (0.9) | 4.2 (0.8) | 0.02 |
| Cigarette use | | | |
| Ever smoked (%) | 76 | 54 | 0.0001 |
| Pack-years (no.) | 23.2 (1.9) | 17.5 (1.7) | 0.03 |
| Use NSAIDs¶ (%) | 20 | 30 | 0.02 |
| Physical activity | | | |
| Moderate-vigorous MET¶-hours/day | 27.6 (1.4) | 30.2 (1.3) | 0.10 |
| Dietary intake | | | |
| Total energy (kcal/day) | 2,008 (60) | 2,044 (53) | 0.67# |
| Fat energy (% kcal) | 32.2 (0.6) | 31.3 (0.5) | 0.21 |
| Protein energy (% kcal) | 17.1 (0.3) | 17.0 (0.3) | 0.84 |
| Carbohydrate energy (% kcal) | 52.8 (0.7) | 55.1 (0.6) | 0.02 |
| Fruits and vegetables (servings/day) | 6.2 (0.3) | 6.5 (0.3) | 0.69# |
| Red meat (servings/day) | 4.9 (0.4) | 4.1 (0.3) | 0.25# |
| Total calcium (mg/day) | 743 (33.0) | 825 (29.0) | 0.07# |
| Sucrose (g/day) | 48 (2) | 55 (2) | 0.01# |
| Anthropometrics | | | |
| Height (m) | 1.72 (0.1) | 1.69 (0.00) | 0.003 |
| Weight (kg) | 80.8 (1.2) | 78.7 (1.1) | 0.20 |
| Body mass index (kg/m²) | 27.3 (0.4) | 27.2 (0.4) | 0.81 |
| Waist circumference (cm) | 96.9 (1.1) | 94.8 (1.0) | 0.17 |
| Waist/hip ratio | 0.92 (0.01) | 0.91 (0.01) | 0.10 |

* Unless otherwise indicated, values are mean (standard error).
† Continuous variables are adjusted for age and sex. Age is adjusted for sex.
‡ Analysis of covariance for continuous variables and chi-square test of proportions for categorical variables.
§ History of colorectal cancer in a first-degree relative.
¶ NSAIDs, regular use of nonsteroidal antiinflammatory drugs, excluding aspirin; MET, metabolic equivalent.
# p value for the transformed dietary variable comparisons.
## TABLE 2.  Associations of physical activity, total energy intake, anthropometrics, and use of nonsteroidal antiinflammatory drugs excluding aspirin with incident sporadic adenomas (n = 405; men: n = 189; women: n = 216), Markers for Adenomatous Polyps Study, 1995–1997

<table>
<thead>
<tr>
<th>Risk factors*</th>
<th>Crude associations†</th>
<th>Multivariate associations‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Moderate-vigorous physical activity (MET§-hours/day)</td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>0.60</td>
<td>0.34, 1.06</td>
</tr>
<tr>
<td>3</td>
<td>0.45</td>
<td>0.25, 0.83</td>
</tr>
<tr>
<td>4</td>
<td>0.61</td>
<td>0.35, 1.06</td>
</tr>
<tr>
<td>$\rho_{\text{rand}}$</td>
<td>0.08</td>
<td>0.13</td>
</tr>
<tr>
<td>Total energy intake (kcal/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>1.05</td>
<td>0.60, 1.83</td>
</tr>
<tr>
<td>3</td>
<td>0.90</td>
<td>0.41, 1.60</td>
</tr>
<tr>
<td>4</td>
<td>0.69</td>
<td>0.38, 1.25</td>
</tr>
<tr>
<td>$\rho_{\text{rand}}$</td>
<td>0.15</td>
<td>0.47</td>
</tr>
<tr>
<td>Anthropometrics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>0.67</td>
<td>0.38, 1.19</td>
</tr>
<tr>
<td>3</td>
<td>0.60</td>
<td>0.34, 1.08</td>
</tr>
<tr>
<td>4</td>
<td>0.97</td>
<td>0.56, 1.68</td>
</tr>
<tr>
<td>$\rho_{\text{rand}}$</td>
<td>0.71</td>
<td>0.59</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>0.72</td>
<td>0.38, 1.36</td>
</tr>
<tr>
<td>3</td>
<td>1.14</td>
<td>0.64, 2.23</td>
</tr>
<tr>
<td>4</td>
<td>1.37</td>
<td>0.77, 2.42</td>
</tr>
<tr>
<td>$\rho_{\text{rand}}$</td>
<td>0.13</td>
<td>0.14</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>0.72</td>
<td>0.39, 1.34</td>
</tr>
<tr>
<td>3</td>
<td>0.91</td>
<td>0.51, 1.62</td>
</tr>
<tr>
<td>4</td>
<td>1.20</td>
<td>0.68, 2.11</td>
</tr>
<tr>
<td>$\rho_{\text{rand}}$</td>
<td>0.25</td>
<td>0.77</td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>1.43</td>
<td>0.76, 2.67</td>
</tr>
<tr>
<td>3</td>
<td>2.27</td>
<td>1.27, 4.04</td>
</tr>
<tr>
<td>4</td>
<td>2.22</td>
<td>1.23, 4.02</td>
</tr>
<tr>
<td>$\rho_{\text{rand}}$</td>
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<td>0.001</td>
</tr>
<tr>
<td>NSAID§</td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>0.70</td>
<td>0.43, 1.14</td>
</tr>
</tbody>
</table>

* Cutpoints for quartiles from low to high were as follows: 17.1, 28.3, and 40.0 metabolic equivalent-hours/day for physical activity; 1,684, 2,223, and 2,768 kcal/day for total energy intake among men and 1,358, 1,746, and 2,137 kcal/day among women; 25.1, 27.1, and 29.5 kg/m² for body mass index among men and 22.7, 25.2, and 30.0 kg/m² among women; 0.95, 0.98, and 1.02 for waist/hip ratio among men and 0.78, 0.83, and 0.88 among women; 95.9, 99.7, and 108.0 cm for waist circumference among men and 77.5, 87.0, and 99.7 cm among women; 1.73, 1.77, and 1.83 m for height among men and 1.57, 1.63, and 1.68 m among women. Quartiles for total energy intake and the anthropometrics were based on the sex-specific distributions among controls.

† Adjusted for sex and age.

‡ Covariates for all models include physical activity, total energy intake, body mass index, waist/hip ratio, height, sex, age, pack-years of smoking, regular use of nonsteroidal antiinflammatory drugs, history of colorectal cancer in a first-degree relative, daily intake of sucrose, and daily intake of calcium. Model for waist circumference does not include body mass index or waist/hip ratio.

§ CI, confidence interval; MET, metabolic equivalent; NSAID, regular use of nonsteroidal antiinflammatory drugs excluding aspirin.
sizes in the stratified analyses may have contributed to null findings for these tests of interaction. However, the patterns in these data suggest that physical activity may have its greatest effect in reducing adenoma risk among persons with a short stature or low waist/hip ratio who also report higher energy intakes. In the analysis of the joint and combined associations for physical activity, waist/hip ratio, and height, it appears that physical activity has its greatest effect in reducing adenoma risk for shorter individuals whether the waist/hip ratio is high or low. These observations suggest that multiple factors influencing energy consumption and energy expenditure may contribute to this lowering of risk of adenoma.

In addition to the more obvious explanation that those who expend more energy through activity can consume more energy and yet maintain energy balance, these data suggest that physical activity may have a greater effect on specific body phenotypes, namely, those with short stature or small waist/hip ratio who also consume more energy. Individual differences in energy expenditure may affect energy balance, enabling, for example, some individuals to consume higher levels of energy and yet maintain a low waist/hip ratio. These may include differences in fat-free mass, age, sex, spontaneous physical activity, sympathetic nervous system activity, leptin secretion and resistance, sex hormone activity, and central nervous system activity in regulation of food intake (27, 28).

The inverse physical activity-adenoma association noted in the present study has been described previously. Of seven studies (17, 29–34) reviewed that evaluated the association between physical activity and adenoma, five (30–34) reported a significant inverse association. In a review of physical activity and colorectal cancer, Colditz et al. (7) reported that physical activity has been consistently associated with a reduction in risk of colon cancer and that there is a dose-response relation.

Though reported studies of adenoma and colorectal cancer have generally found an increased adenoma risk with higher total energy intake (13, 18, 32, 35–38), the inverse association noted in this study has also been reported (12, 31, 39, 40). Findings from animal studies, however, have consistently documented an increased risk of chemically induced colon cancer with increased energy intake, independent of the fat content of the diet (41–45). The inverse association

### Table 3
Multivariate-adjusted associations of physical activity with incident sporadic adenoma according to use of nonsteroidal antiinflammatory drugs excluding aspirin, Markers of Adenomatous Polyps Study, 1995–1997*

<table>
<thead>
<tr>
<th>NSAID†</th>
<th>Physical activity (MET‡-hours/day)‡</th>
<th>Low Odds ratio 95% CI†</th>
<th>Medium Odds ratio 95% CI†</th>
<th>High Odds ratio 95% CI†</th>
<th>ρrend</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>1.00§</td>
<td>0.37</td>
<td>0.19, 0.72</td>
<td>0.49</td>
<td>0.25, 0.94</td>
</tr>
<tr>
<td>Yes</td>
<td>1.00</td>
<td>1.75</td>
<td>0.40, 7.65</td>
<td>1.75</td>
<td>0.49, 6.20</td>
</tr>
</tbody>
</table>

* Covariates include total energy intake, body mass index, waist/hip ratio, height, sex, age, pack-years of smoking, history of colorectal cancer in a first-degree relative, daily intake of sucrose, and daily intake of calcium.
† NSAID, nonsteroidal antiinflammatory drug use excluding aspirin; MET, metabolic equivalent; CI, confidence interval.
‡ “Low,” “medium,” and “high” represent tertiles of physical activity.
§ Referent.

### Table 4
Joint and combined effects between physical activity and selected anthropometrics (waist/hip ratio and height) on risk of incident sporadic adenomas, Markers of Adenomatous Polyps Study, 1995–1997†

<table>
<thead>
<tr>
<th>Moderate-vigorous physical activity (MET‡-hours/day)</th>
<th>Waist/hip ratio</th>
<th></th>
<th>Height</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Odds ratio 95% CI†</td>
<td>Odds ratio 95% CI†</td>
<td>Odds ratio 95% CI†</td>
</tr>
<tr>
<td>≤28.3</td>
<td>1.00</td>
<td>0.51, 0.26, 0.99</td>
<td>1.00</td>
</tr>
<tr>
<td>&gt;28.3</td>
<td>0.53, 0.29, 0.97</td>
<td>0.37, 0.18, 0.75</td>
<td>0.78, 0.42, 1.45</td>
</tr>
</tbody>
</table>

* Covariates include sex, age, body mass index, pack-years of smoking, use of nonsteroidal antiinflammatory drugs, history of colorectal cancer in a first-degree relative, daily intake of sucrose, daily intake of calcium, and total energy intake. Depending on the model, waist/hip ratio or height is also included.
† All variables are dichotomized on medians for controls. Medians are sex specific except for physical activity. Medians for variables are as follows: physical activity: 27 metabolic equivalent-hours/day; waist/hip ratio: men = 0.98; women = 0.83; height: men = 1.77 m; women = 1.63 m.
‡ MET, metabolic equivalent; CI, confidence interval.
described in this and other studies may be an indirect measure of energy expenditure, whereby those who consume more total energy do so because they expend more energy through higher levels of physical activity (14). These qualitative and quantitative differences in estimated risk may also be related to differences in study design, recall bias in self-reported dietary data, population differences in patterns of energy intake, or distribution of other related risk factors such as physical activity.

Body mass index is an indicator of long-term energy balance, as are waist circumference and waist/hip ratio, which are more specifically indicators of central adiposity (46, 47). In this study, only waist/hip ratio was found to be consistently associated with adenoma risk, with this association being stronger for large adenomas (>1 cm in diameter; data not shown). These findings are supported by at least two other studies reporting an increased risk for larger adenomas with greater waist/hip ratio (17, 48), and they add support to the hypothesis that central obesity may be an independent risk factor of adenoma. This hypothesis has been supported by at least three studies that reported an increased risk of colorectal cancer with higher levels of waist/hip ratio (15, 17, 49).

Although strongly influenced by genetics, height is also an index of nutritional status and energy intake during childhood (50, 51). In adults, it is related to social class and may influence...
enone other exposures, including health-related behaviors, psychosocial influences, and environmental factors. In a large prospective study, Jousilahti et al. (52) found that height was directly associated with mortality from some organ-specific cancers including the rectum. Smith et al. (51) also reported that mortality from non-smoking-related cancers, especially colorectal and prostate cancers, tends to increase with height. Findings of the direct height-adenoma association reported in this study are supported by other studies that have reported a similar association between height and adenomas or colonic neoplasms (17, 53). It has been suggested that a childhood diet resulting in higher stature may produce higher concentrations of insulin-like growth factor I that stimulates cell proliferation and may protect genetically damaged cells from apoptosis (54). It has also been hypothesized that, since adult stature correlates closely with the length of the colon, greater height increases the total number of stem cells ultimately at risk for transformation (17).

Height and waist/hip ratio may represent multiple pathways that influence risk of adenoma. Height may reflect energy intake during childhood and adolescence, the complex genetic makeup of the individual related to metabolism and energy balance, or both. The waist/hip ratio may also reflect this complex genetic makeup or the individual’s long-term energy balance. If height and waist/hip ratio are indicators of genetic makeup, physical activity may interact with them in some way, allowing physical activity to have a greater effect for individuals who are shorter or thinner.

The influences of physical activity, total energy intake, and positive energy balance that result in a higher waist/hip ratio most likely relate to multiple biologic mechanisms that affect risk of colorectal cancer. One unifying hypothesis with increasing support suggests that physical activity and central obesity are each related independently to insulin resistance (55). Diets high in fat and energy and low in complex carbohydrates, in combination with a physically inactive lifestyle, can lead to changes in an individual’s lipid-lipoprotein metabolism that have been collectively termed the “insulin resistance syndrome” (56–58). The primary components of this syndrome are central obesity, hypertension, insulin resistance, glucose intolerance or type II diabetes mellitus, hypertriglyceridemia, and dyslipidemia (59–61). Concentrations of insulin and insulin-like growth factor I are also increased. As insulin is a growth factor for colonic mucosal cells and colonic carcinoma cells in vitro (62–64), high serum concentrations in humans may promote growth of colon tumors, stimulate insulin-like growth factor receptors, and act as a cell mitogen. Insulin-like growth factor I is required for mitosis in some cell types (65), and it also inhibits c-myc-induced apoptosis (66, 67). Colonic cancer tissue has both insulin and insulin-like growth factor I receptors through which insulin has been shown to exert its mitogenic effect (62).

A parallel hypothesis for the inverse association of physical activity and energy balance with adenoma risk involves the effect of these exposures on prostaglandin levels and subsequent colon cell proliferation. Serum levels of prostaglandin E2, which has an antiapoptotic effect on colonic epithelial cells, decrease with increased physical activity (68), which may result in reduced prostaglandin E2 in rectal mucosa (21). To the contrary, levels of prostaglandin F2, which decreases the rate of colonic cell division, increase with greater physical activity (8). Interestingly, the mechanism of action for NSAIDs is the inhibition of cyclooxygenase, which catalyzes the synthesis of prostaglandins (69). Individuals with higher body mass index levels have been reported to have higher rectal prostaglandin E2 levels (21), perhaps due to upregulation of cyclooxygenase-2 by inflammatory cytokines derived from adipose tissue (70). In a large case-control study (71), the strength of the colon cancer-physical activity association was somewhat stronger among those who did not take NSAIDs, suggesting potential effect modification with NSAID use. In the present study, the inverse association of physical activity and adenoma risk was not apparent in those using NSAIDs regularly. The beneficial effects of NSAIDs to reduce colon carcinogenesis by blocking the action of cyclooxygenase-2 may have been so strong in NSAID users that the beneficial effects of physical activity, working through similar mechanisms to affect prostaglandins, were not apparent.

The primary strengths of this study are the ability to examine the association of adenoma with the primary components of energy balance, measures of long-term energy balance, and NSAID use; exposure assessment prior to diagnosis of endpoint; and complete colon evaluation of both cases and controls. However, even though our key findings are biologically plausible and the risk estimates are in the directions hypothesized and in most cases statistically significant, given the multiple comparisons and the relatively small sample size with consequent wide confidence intervals in the stratified analyses, the present results should be interpreted cautiously.

Methodological limitations are inherent in the design of community- and colonoscopy-based, case-control studies of colorectal adenoma. This includes the selection of controls from among individuals who may be referred for colonoscopy with signs and symptoms that suggest higher risk of colorectal neoplasms. In the context of our behavioral exposures, the most likely influence on our results would be that controls would be more similar to cases, which could lead to an underestimate of the true risk of adenoma. Limitations in all behavioral epidemiologic studies include the difficulty in accurately measuring total energy intake and energy expenditure (physical activity) using self-reported measures. Although this study relied on self-reported measures for the anthropometrics, this methodology has been previously validated (40). It is possible that imprecision in these measures resulted in attenuation of the true risk of adenoma associated with these exposures and may have contributed to the lack of significant findings for total energy intake, body mass index, and waist circumference. In contrast, the strengths of this investigation are that controls were selected from the population that gave rise to the cases, and the potential for differential reporting bias was limited by obtaining self-reports of exposure prior to colonoscopy and the diagnosis of adenoma.

In conclusion, this case-control study provides additional evidence, particularly among women, that higher levels of physical activity and overall energy balance are associated with adenoma risk. Importantly, our finding that the effect of physical activity on adenoma risk was found only among...
those not using NSAIDs suggests that physical activity’s effect on adenomas may operate through inflammatory mechanisms.

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REFERENCES

39. Neugut AI, Garbowski GC, Lee WC, et al. Dietary risk factors...