Energy Balance and Colon Cancer – beyond Physical Activity

Martha L. Slattery, John Potter, Bette Caan, Sandra Edwards, Ashley Coates, Khe-Ni Ma, and T. Dennis Berry

INTRODUCTION

The incidence of colon cancer is higher in Westernized countries than in other parts of the world (1, 2). A Western lifestyle, including being physically inactive and consuming more energy than is needed for a given activity level and the subsequent increases in body weight, is thought to contribute to the high rates of colon cancer that are observed. Of these factors, physical activity has been consistently shown, in both case-control and cohort studies and in studies of occupational and leisure-time activity, to be associated with a lower risk of developing colon cancer (3–12). Being physically active has been consistently associated with lower risk of colon cancer, but high energy intake and a large body size have been associated with higher risk of colon cancer in only some studies (13). Researchers who have shown that energy intake is not directly associated with colon cancer have postulated that energy intake is a surrogate for level of physical activity, as it is with coronary heart disease (14–16).

However, there are limited data that have evaluated the combined associations of physical activity, energy intake, and body size with colon cancer. Physical activity has been shown to modify the risk associated with energy intake (4, 17). On the other hand, the combined effects of all three factors (physical activity, energy intake, and body size) in the energy balance equation are unknown. It is most likely that these lifestyle factors work in concert to determine the actual colon cancer risk observed; there are reasons to believe that such associations exist (18). Thus, the purpose of this study is to evaluate the associations between components of energy balance and colon cancer. We do this by evaluating the independent and combined effects of physical activity, energy intake, and body mass in a large case-control study of colon cancer.

MATERIALS AND METHODS

Study Population. Participants in the study were from the Kaiser Permanente Medical Care Program of northern California, an eight-county area in Utah (Davis, Salt Lake, Utah, Weber, Wasatch, Tooele, Morgan, and Summit counties), and the metropolitan Twin Cities area (Anoka, Carver, Dakota, Hennepin, Ramsey, Scott, and Washington counties) in Minnesota. All eligible cases within these defined geographic areas were identified. Controls were matched to cases by sex and by 5-year age groups. The study population was 91.3% white, 4.2% black, and 4.4% Hispanic as reported at the time of interview.

Eligibility criteria included cases that were: (a) diagnosed with first primary colon cancer (International Classification of Diseases of Oncology second edition codes 18.0 and 18.2–18.9) between October 1, 1991 and September 30, 1994; (b) between 30 and 79 years of age at time of diagnosis; (c) English-speaking; and (d) mentally competent to complete the interview. Cases with tumors in the rectosigmoid junction or rectum were not eligible. Cases with known (as indicated on the pathology report) familial adenomatous polyposis, ulcerative colitis, or Crohn’s disease also were not eligible. A rapid-reporting system was used to identify cases, with the majority of cases being interviewed within 4 months of diagnosis. Despite our rapid case identification, 342 (10.6%) of the 3230 cases identified were deceased or too ill to complete the interview. Another 157 (4.9%) cases were not contacted because physicians denied permission. Twenty-nine (0.9%) cases had moved before we were able to interview them, and we were unable to locate 77 cases (2.4%). Of those we identified and asked to participate, 75.6% cooperated. Of the 4656 controls selected (19), 51 (1.1%) were deceased or too ill to complete the interview, 13 (0.3%) were known to have moved, and 752 (16.2%) were not contacted or were unable to be located. Of these, 663 were driver’s license controls from Minnesota, where new license holders were added on a regular basis, although the names of people who died or moved were not purged from the register. For the entire study, we interviewed 63.7% of the controls we contacted. A total of 2280 cases and 2494 controls were interviewed. Of these, 197 cases and 18 controls were excluded because they were found to be ineligible, and 90 cases and 66 controls were excluded from the analysis because they reported Crohn’s disease or ulcerative colitis at the interview or had missing data or data were considered to be of poor quality by the interviewer. A total of 1993 cases and 2410 controls are included in the analyses presented.
Physical Activity. Study participants were asked to recall their activity patterns at home, leisure, and work for the referent year as well as 10 and 20 years ago. Physical activity performed at home and at leisure was ascertained using an adaptation of the CARDIA physical activity history (21); respondents were asked to recall their activity for the referent year. Participants were asked if they performed moderate and vigorous activities for at least 1-h total time in any month of the referent year. There were eight categories of vigorous activities, which were defined as "those activities which make you sweat or get out of breath," and four questions about moderate-level activities, which were defined as "those which are done at a more moderate pace than more strenuous activities." Cue cards, which listed examples of moderate and vigorous activities, were used to assist participants in recalling their moderate and vigorous activities done at leisure, home, and work. Participants were asked how many months they performed each activity, the average amount of time performed per session, and the usual number of days per week or month that the activity was performed. We have previously evaluated ability to recall past activity (2–3 years ago) using the CARDIA physical activity questionnaire and have found that recall of activity is extremely high when compared to that reported 2–3 years ago (r for total activity = 0.81; r for vigorous activity = 0.84; Ref. 22).

The total amount of time spent in physical activities was converted to caloric expenditure as described by Taylor et al. (23). Moderate-level activities were assigned 4.5 kcal/min, and intense activities were assigned 5.5–6.5 kcal/min. This was done so that various categories of activity could be combined into summary variables. We created lifetime activity variables that incorporated those leisure and home activities performed during the referent year, 10 years ago, and 20 years ago. For each time period (referent year, 10 years ago, and 20 years ago), participants were given a rank order from 1–4, with a rank of 1 being the lowest level of reported activity and a rank of 4 being the highest level of reported activity. For example, for vigorous activity, a rank of 1 indicated no vigorous activity, a rank of 2 indicated 1–250 kcal/week were expended in vigorous activities, a rank of 3 indicated 250–1000 kcal/week were expended in vigorous activities, and a rank of 4 was given to those participants who reported that over 1000 kcal/week of energy were expended in vigorous activity. Because participants who were less than 40 were not asked to recall their activity levels before age 20, activity levels reported 10 years ago were weighted twice in establishing an average lifetime activity index. In the analyses presented below, we use lifetime vigorous leisure-time activity because it seemed to be the physical activity variable most consistently associated with colon cancer (24).

Dietary Intake. Dietary intake was ascertained using an adaptation of the CARDIA diet history (25–27). Participants were asked to recall foods eaten, the frequency with which they were eaten, serving size, and whether fats were added in the preparation. As part of the diet history, detailed information was obtained on foods eaten as additions to other foods. Foods eaten away from home were ascertained, and those prepared with fat were assigned the fat most commonly used at a medium-priced restaurant. Nutrient information was obtained by converting food-intake data into nutrient data using the Minnesota Nutrition Coordinating Center nutrient database (28).

Body Size. Height was measured at the time of interview, and weight was reported for the referent period. BMI was calculated as weight/height^2 for men and weight/height^1.5 for women. Weight/height^1.5 has been shown to be more independent of height among women than weight/height^2 (29) and is used as the primary indicator of body mass among women.

Statistical Methods. Unconditional logistic regression models were used to estimate risk of colon cancer from physical activity, energy intake, and BMI. In these models, the following variables were included: (a) age at selection; (b) BMI; (c) recalled family history of colorectal cancer in first-degree relatives; (d) physical activity; (e) energy intake; (f) dietary fiber; (g) dietary calcium; (h) dietary cholesterol; and (i) use of aspirin and/or nonsteroidal anti-inflammatory drugs on a regular basis. Age-specific analyses were performed using age 67 as a cutpoint because this was the median age of the control population. Tumor site within the colon was defined as proximal (cecum through transverse colon) or distal (splenic flexure, descending, and sigmoid colon). Interactions among physical activity, BMI, dietary energy, and other variables were assessed using categorical variables. Statistical assessment of multiplicative interaction was done by taking ~2X the difference in the log likelihood of the model with and without the categorical interaction term (30).

RESULTS

Cases and controls were comparable in terms of religious preference and level of income, however, male controls tended to be better educated than male cases (Table 1). Among women, there were no case-control differences in the demographic characteristics of the population. Cases tended to be less physically active, to consume more energy, and to have slightly large BMIs. Participants who reported more lifetime vigorous leisure-time physical activity tended to have lower BMI levels (data not shown). Although both cases and controls consumed more energy with increasing level of physical activity, for most activity levels, cases consumed more energy per level of physical activity than did controls. There were no differences in the percentage of total energy from fat, protein, and carbohydrates by level of physical activity among cases and controls or between cases and controls.

Lack of lifetime involvement in vigorous leisure-time activity was associated with increased risk of colon cancer in both men and women (Table 2). Further evaluation of lifetime vigorous leisure-time activity by age and tumor site for men and women showed very consistent results across all ages and tumor sites, with an approximately 60% increase in risk among those who reported no activity compared to those who reported high levels of lifetime vigorous leisure-time activity during the past 20 years of their lives. Because of interest in the role of vitamin D in colon cancer, we also adjusted for the total number of hours spent outdoors during the year to determine if the association between colon cancer and physical activity was confounded by exposure to sunshine (31). For men, the sunshine exposure-adjusted risk estimate was 1.59 compared to 1.63 when sunshine exposure was not in the model; for women, the risk estimate was unchanged.

Higher levels of energy intake were associated with increased risk of colon cancer, comparing the highest to lowest levels of intake (Table 3). Associations were generally stronger for people diagnosed at a younger age rather than at an older age. Among older men and women, being in the upper quintile of energy intake was not significantly associated with colon cancer risk. Among women, associations were slightly stronger for tumors in the proximal colon.

BMI was associated with a greater risk of colon cancer among men than among women (Table 4). Associations were strongest for younger men and those with distal tumors. Higher levels of BMI were associated with a 60% increased risk of colon cancer among younger women (95% CI, 1.06–2.37) and those with distal tumors (95% CI, 1.12–2.32). Women who were older at the time of diagnosis or who had proximal tumors showed only a slightly elevated risk of colon cancer associated with a large BMI. The association between weight/height^1.5 and colon cancer among women was similar to that observed using the more standard weight/height^2 [ORs across quintile of the total population relative to the lowest quintile were 1.20 (95% CI, 0.90–1.61); 1.29 (95% CI, 0.96–1.73); 1.31 (95% CI, 0.97–1.75); and 1.44 (95% CI, 1.08–1.93)].

In the two-way stratifications, the ORs associated with lower activity in the presence of higher BMI, higher energy intake in the presence of lower activity, and higher energy intake in the presence of higher BMI showed similar patterns. Those with higher activity levels

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76
Table 1 Description of study population

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<tr>
<th>Center</th>
<th>Cases</th>
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<th>Controls</th>
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<th>N (%)</th>
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<td>Catholic</td>
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<td>Protestant</td>
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<td>387</td>
<td>480 (46.2)</td>
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<td>57</td>
<td>59 (5.7)</td>
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<td>$20,000-$35,000</td>
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<tr>
<td>$35,000-$60,000</td>
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<td>443</td>
<td>705</td>
<td>292 (29.0)</td>
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<td>&gt;$60,000</td>
<td>176 (16.9)</td>
<td>256</td>
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<th>Controls</th>
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<td>None</td>
<td>233 (21.3)</td>
<td>216</td>
<td>324</td>
<td>314 (28.2)</td>
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</tr>
<tr>
<td>2</td>
<td>311 (28.4)</td>
<td>314</td>
<td>231</td>
<td>313 (28.1)</td>
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<td>3</td>
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<td>263 (23.6)</td>
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<tr>
<td>High</td>
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<td>379</td>
<td>145</td>
<td>224 (20.1)</td>
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<table>
<thead>
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<th>BMI (median)</th>
<th>Cases</th>
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<th>N (%)</th>
<th>Controls</th>
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<th>N (%)</th>
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<tbody>
<tr>
<td>None</td>
<td>27.5</td>
<td>26.4</td>
<td>33.0</td>
<td>32.1</td>
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<table>
<thead>
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<th>KCAL (median)</th>
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<th>Controls</th>
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<th>N (%)</th>
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</thead>
<tbody>
<tr>
<td>None</td>
<td>2487</td>
<td>2406</td>
<td>1861</td>
<td>1821</td>
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</table>

a $P$ was obtained from t test comparing the difference in means between cases and controls. Other $P$ values are from $\chi^2$ test comparing differences in distributions between cases and controls.

b BMI, weight/height$^2$ for men and weight/height$^{1.5}$ for women.

tended to be at lower risk irrespective of the other variable, and the pattern was more marked in men than women (Table 5). Inclusion of an interaction term for energy intake and physical activity in the model marginally improved the overall fit ($P = 0.10$) for distal tumors among men and for older men and women ($P = 0.05$) although the colon cancer risk associated with both physical activity and high BMI levels was greater than would be expected on either an additive or multiplicative model, inclusion of an interaction term for physical activity and BMI only significantly improved the overall fit of the model at the 0.05 level for younger women and those with proximal tumors.

Data are presented that combine various levels of physical activity [categorized as low, intermediate (groups 2 and 3 from Table 2), or high levels of lifetime vigorous activity], BMI (categorized by tertiles of BMI for men and women separately as shown in Table 5), and energy intake (bottom two-thirds of the distribution compared to the highest tertile for men and women). Participants who reported no vigorous activity, consumed high levels of energy, and had a large

Table 2 Association between lifetime vigorous activity and colon cancer

<table>
<thead>
<tr>
<th>All subjects</th>
<th>&lt;67 yrs</th>
<th>≥67 yrs</th>
<th>Distal</th>
<th>Proximal</th>
</tr>
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<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10—12</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>7—9</td>
<td>1.60 (1.11–1.75)</td>
<td>1.58 (1.16–1.26)</td>
<td>1.19 (0.85–1.67)</td>
<td>1.36 (1.02–1.81)</td>
</tr>
<tr>
<td>4—6</td>
<td>1.59 (1.26–2.01)</td>
<td>1.49 (1.07–2.07)</td>
<td>1.68 (1.20–2.37)</td>
<td>1.43 (1.07–1.92)</td>
</tr>
<tr>
<td>&lt;4</td>
<td>1.63 (1.26–2.12)</td>
<td>1.69 (1.23–2.51)</td>
<td>1.58 (1.11–2.23)</td>
<td>1.53 (1.12–2.11)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAI</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>10—12</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>7—9</td>
<td>1.14 (0.86–1.52)</td>
<td>1.19 (0.82–1.72)</td>
<td>1.07 (0.67–1.71)</td>
<td>1.17 (0.81–1.67)</td>
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<tr>
<td>4—6</td>
<td>1.13 (0.85–1.49)</td>
<td>1.22 (0.85–1.75)</td>
<td>1.00 (0.64–1.56)</td>
<td>1.08 (0.76–1.53)</td>
</tr>
<tr>
<td>&lt;4</td>
<td>1.59 (1.21–2.10)</td>
<td>1.62 (1.10–2.37)</td>
<td>1.57 (1.02–2.39)</td>
<td>1.60 (1.13–2.26)</td>
</tr>
</tbody>
</table>

a Risk estimates adjusted for age, BMI, family history of first-degree relative with colorectal cancer, use of aspirin and/or nonsteroidal anti-inflammatory drugs, energy intake, and dietary intake of fiber and calcium. PAI, physical activity index (PAI < 4, no vigorous activity).
Table 3 Association between energy intake and colon cancer

<table>
<thead>
<tr>
<th></th>
<th>All subjects</th>
<th>&lt;67 yrs</th>
<th>67 yrs</th>
<th>Distal OR (95% CI)</th>
<th>Proximal OR (95% CI)</th>
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<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kcal/day</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>&lt;1809</td>
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<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1809-2233</td>
<td>1.12 (0.85-1.49)</td>
<td>1.17 (0.76-1.81)</td>
<td>1.11 (0.82-1.68)</td>
<td>1.15 (0.81-1.64)</td>
<td>1.07 (0.76-1.52)</td>
</tr>
<tr>
<td>2234-2730</td>
<td>1.37 (1.03-1.83)</td>
<td>1.48 (0.96-2.28)</td>
<td>1.32 (0.99-2.15)</td>
<td>1.27 (0.88-1.64)</td>
<td>1.42 (0.99-2.04)</td>
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<td>&gt;2731</td>
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<td>1.43 (0.91-2.25)</td>
<td>1.53 (1.13-2.76)</td>
<td>1.54 (1.04-2.28)</td>
<td>1.40 (0.94-2.09)</td>
</tr>
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<td><strong>Women</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kcal/day</td>
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<td>&lt;1369</td>
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<td>1369-1690</td>
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<td>1.75 (1.11-2.77)</td>
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<td>1.49 (1.01-2.19)</td>
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<tr>
<td>&gt;2070</td>
<td>1.00 (1.07-2.70)</td>
<td>1.27 (0.77-2.10)</td>
<td>0.87 (0.51-1.47)</td>
<td>1.03 (0.65-1.62)</td>
<td>1.06 (0.66-1.63)</td>
</tr>
</tbody>
</table>

Risk estimates adjusted for age, BMI, family history of first-degree relative with colorectal cancer, use of aspirin and/or nonsteroidal anti-inflammatory drugs, physical activity, and dietary intake of fiber, cholesterol, and calcium.

Table 4 Association between BMI and colon cancer

<table>
<thead>
<tr>
<th></th>
<th>All subjects</th>
<th>&lt;67 yrs</th>
<th>67 yrs</th>
<th>Distal OR (95% CI)</th>
<th>Proximal OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI &lt;23.75</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>23.75-25.54</td>
<td>1.23 (0.93-1.63)</td>
<td>1.33 (0.88-2.02)</td>
<td>1.15 (0.78-1.69)</td>
<td>1.37 (0.95-1.98)</td>
<td>1.14 (0.80-1.64)</td>
</tr>
<tr>
<td>25.55-27.31</td>
<td>1.32 (1.00-1.74)</td>
<td>1.46 (0.98-2.19)</td>
<td>1.22 (0.82-1.80)</td>
<td>1.52 (1.06-2.17)</td>
<td>1.20 (0.84-1.71)</td>
</tr>
<tr>
<td>&gt;27.31</td>
<td>1.78 (1.36-2.33)</td>
<td>1.89 (1.28-2.80)</td>
<td>1.67 (1.15-2.42)</td>
<td>1.88 (1.33-2.67)</td>
<td>1.71 (1.22-2.39)</td>
</tr>
</tbody>
</table>

**Women**

| BMI <28.01| 1.00         | 1.00    | 1.00   | 1.00              | 1.00                |
| 28.01-30.99| 1.26 (0.94-1.68) | 0.95 (0.63-1.44) | 1.66 (1.09-2.53) | 1.21 (0.83-1.77) | 1.33 (0.92-1.92) |
| 31.00-33.81| 1.19 (0.89-1.60) | 1.13 (0.74-1.72) | 1.22 (0.80-1.86) | 1.23 (0.84-1.79) | 1.26 (0.87-1.83) |
| >33.82    | 1.45 (1.08-1.94) | 1.57 (1.05-2.35) | 1.27 (0.82-1.96) | 1.63 (1.13-2.35) | 1.28 (0.87-1.86) |

Risk estimates adjusted for age, energy intake, family history of first degree relative with colorectal cancer, use of aspirin and/or nonsteroidal anti-inflammatory drugs, physical activity, dietary intake of fiber and calcium.

BMI were at higher risk than those who were active, consumed low levels of energy, and had low BMIs (Table 6). The pattern of associations between risk of colon cancer and physical activity, energy intake, and BMI was similar in men and women, although overall, unfavorable energy balance seems to have more of an effect in men (OR, 7.22; 95% CI, 3.42-15.2) than in women (OR, 1.61; 95% CI, 0.84-3.09); estimates were less precise when sex-specific analyses were done. The overall patterns of associations when examining separately those under or over age 67 or those with proximal versus distal colon tumors were not substantially different. When we examin-
NERGY BALANCE AND COLON CANCER

Table 6 Interaction between lifetime vigorous leisure-time physical activity, energy intake, and BMI^a

<table>
<thead>
<tr>
<th>Physical activity</th>
<th>Energy intake</th>
<th>Low (OR [95% CI])</th>
<th>Intermediate (OR [95% CI])</th>
<th>High (OR [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>Low</td>
<td>1.00</td>
<td>1.06 (0.71—1.59)</td>
<td>1.10 (0.74—1.64)</td>
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<tr>
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<td>High</td>
<td>1.24 (0.78—2.00)</td>
<td>1.32 (0.80—2.20)</td>
<td>1.28 (0.81—2.03)</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>1.34 (0.97—1.84)</td>
<td>1.34 (0.97—1.84)</td>
<td>1.86 (1.36—2.56)</td>
</tr>
<tr>
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<td>Low</td>
<td>1.60 (1.05—2.42)</td>
<td>1.45 (0.96—2.19)</td>
<td>2.21 (1.50—3.26)</td>
</tr>
<tr>
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<td>High</td>
<td>1.36 (0.94—1.98)</td>
<td>1.52 (1.06—2.24)</td>
<td>2.07 (1.45—2.95)</td>
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<tr>
<td></td>
<td></td>
<td>2.00 (1.14—3.50)</td>
<td>2.19 (1.23—3.90)</td>
<td>3.35 (2.09—5.35)</td>
</tr>
<tr>
<td>Men</td>
<td>High</td>
<td>1.00</td>
<td>1.24 (0.74—2.08)</td>
<td>1.61 (0.96—2.71)</td>
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<tr>
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<td>Low</td>
<td>1.73 (0.92—3.23)</td>
<td>1.73 (0.89—3.38)</td>
<td>1.86 (1.03—3.35)</td>
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<td>Intermediate</td>
<td>1.40 (0.91—2.17)</td>
<td>1.95 (1.28—2.98)</td>
<td>2.88 (1.89—4.38)</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>1.99 (1.14—3.46)</td>
<td>1.93 (1.11—3.35)</td>
<td>2.96 (1.77—4.96)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>1.56 (0.91—2.68)</td>
<td>2.00 (1.17—3.40)</td>
<td>2.35 (1.43—3.86)</td>
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<tr>
<td></td>
<td></td>
<td>2.93 (1.25—6.85)</td>
<td>1.47 (0.53—4.13)</td>
<td>7.22 (3.42—15.2)</td>
</tr>
<tr>
<td>Women</td>
<td>High</td>
<td>1.00</td>
<td>0.88 (0.46—1.70)</td>
<td>0.61 (0.32—1.18)</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>0.76 (0.37—1.58)</td>
<td>0.85 (0.38—1.87)</td>
<td>0.71 (0.32—1.54)</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>0.74 (0.45—1.22)</td>
<td>0.78 (0.47—1.27)</td>
<td>0.99 (0.61—1.63)</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>1.15 (0.58—2.12)</td>
<td>1.95 (0.51—1.79)</td>
<td>1.42 (0.77—2.59)</td>
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<tr>
<td></td>
<td>High</td>
<td>1.01 (0.59—1.73)</td>
<td>1.05 (0.62—1.78)</td>
<td>1.56 (0.92—2.63)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.21 (0.56—2.63)</td>
<td>1.85 (0.87—3.93)</td>
<td>1.61 (0.84—3.09)</td>
</tr>
</tbody>
</table>

^a Risk estimates adjusted for age, family history of first-degree relative with colorectal cancer, use of aspirin and/or nonsteroidal anti-inflammatory drugs, dietary intake of fiber, calcium, and dietary cholesterol, and sex.

ned two-way stratifications by age, sex, and tumor subsite, only among older women (≥67 years) does the pattern become so attenuated as to almost disappear. In this group, the suggestion is that the lowest risk may be seen among women with higher BMI levels. However, even in this group of women, higher levels of physical activity are associated with lower estimates of risk (data not shown).

DISCUSSION

Colon cancer has been shown to increase as people adopt lifestyles that are indigenous in countries that are more Westernized (1, 2). A component of a Westernized lifestyle often includes energy intakes beyond those needed for energy expenditure, resulting in obesity. In this study, we observed that low levels of vigorous lifetime leisure-time activity were associated with an increased risk of colon cancer and that high energy intake and high body mass were associated with increased risk of colon cancer. The associations with physical activity were consistent across sex, age, and tumor-site subgroups. The independent associations with energy intake were weaker among older participants, especially older women; the independent associations with BMI disappeared among older women and women with proximal tumors. However, the presence of any two of the three components of energy balance as risk factors generally resulted in an increased risk of colon cancer beyond that observed for any one factor.

In these data, by examining the combined effects of the three components of energy balance in a pattern that is consistent, we have shown that at high levels of physical activity, risk of colon cancer is not influenced by body mass for both sexes or by higher energy intake among women. Among those whose physical activity is lower, two things change: (a) BMI becomes a more important indicator of risk; and (b) the risk associated with higher energy intake increases. The highest risk is seen for those with the lowest activity, highest BMI, and highest energy intake. This pattern is seen for men and women, among older and younger individuals, and among those with both proximal and distal tumors. However, there seem to be sex differences because the pattern is somewhat less marked in women, and the least convincing evidence is seen in older women. Furthermore, the observation that risk was higher for men than women is supported by migrant studies, which also show that rates of colon cancer go up quicker among men than women when they move from a country in which incidence rates are low to one in which they are high.

Biases could explain this pattern. Associations between physical inactivity and increased risk of colon cancer could be biased from early undiagnosed illness or other related factors among cases. However, we did ask study participants (both cases and controls) if their activity levels were different during the referent year because of illness, injury, or long-term disease. There were no differences between cases and controls in the proportions (5.5% of male controls and 6.9% of male cases and 5.9% of female controls and 5.5% of female cases) who responded that their activity patterns had changed as a result of illness, injury, or long-term disease. Further adjustment for other potential confounders, such as sunshine exposure, did not alter the physical activity/colon cancer association. Dietary data were obtained using a detailed questionnaire. Although there is the possibility in case-control studies that cases recall their diets differently from controls because of illness, we observed similar associations for many dietary factors as reported in cohort studies in which dietary information is obtained before disease (32). However, differences in associations with energy intake in cohort and case-control studies do exist (13) and may have a biological basis rather than one that merely reflects bias. These findings suggest that among those who are physically active, energy intake presents no risk and is in fact protective for women; risk estimates associated with energy intake among men are lower than those observed without consideration of activity level. If cohort studies represent a more physically active cohort than that obtained from a case-control study, differences in observed risk for one factor, such as energy intake, may be the result of differences in the distribution of other risk factors, such as physical activity. Likewise, cohorts of older women, such as the Iowa women’s cohort (33), do not observe an increased risk associated with energy intake. In our population, in which we have the ability to estimate associations by age at diagnosis, we do not observe energy intake to be significantly associated with colon cancer risk among older women. Reported BMI levels were similar to those obtained by measurement at the time of interview. Given the consistency of the findings, there is support that this pattern is real. Is it biologically plausible?

The roles of energy intake, body mass, and physical activity could operate at different levels in the etiology of colon cancer, but the most plausible explanation that unifies the three has to involve metabolic profiles rather than local influences on colonic epithelium. McKeown-Eyssen (18) has proposed that some factors that collectively characterize increased risk (obesity and Western diets) or decreased risk (high complex carbohydrates, vegetables and fruit, and physical activity) may plausibly operate through influences upon serum triglycerides and insulin resistance (syndrome X) more commonly associated with coronary heart disease and diabetes mellitus than colon cancer (18). She argues further that such a metabolic profile may well act as a growth-promotional milieu for cells, thus paralleling, but making more specific, earlier proposals of McMichael and Potter (34, 35). Finally, McKeown-Eyssen (18) proposes that such a growth-promoting milieu might act specifically to benefit neoplastic cells.

These results may be used to help explain differences observed in the literature between energy intake and BMI and colon cancer. In these data, there are clear indications that the association for these factors is somewhat dependent on the level of physical activity of the population. Although studies have attempted in the past to adjust for confounding between physical activity and energy intake or BMI, differences in colon cancer risk in associations with the two latter risk factors across populations may be attributed to differences in the underlying characteristics of populations, including physical activity. In populations in which activity levels are higher, one might expect
associations between energy intake and BMI and colon cancer to be more attenuated than in populations in which levels of physical activity are low.

On the basis of our data, if syndrome X does play a role in colon cancer, the most profound protection may be via maintenance of physical activity. It seems that energy intake slightly increases the risk of colon cancer at all levels of physical activity in men, but that body mass matters only at lower levels of activity. The public health implication is that physical activity is central to reducing risk. It may do so specifically by normalizing the tendency toward the expression of syndrome X, perhaps in a genetically prone but large subset of individuals.

ACKNOWLEDGMENTS

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REFERENCES


Energy Balance and Colon Cancer — beyond Physical Activity
Martha L. Slattery, John Potter, Bette Caan, et al.

*Cancer Res* 1997;57:75-80.

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