Evaluation of Epithelial Cell Proliferation Rate in Normal-appearing Colonic Mucosa as a High-Risk Marker for Colorectal Cancer

Ikuko Akedo, Hideki Ishikawa, Tatuya Ioka, Itaru Kaji, Hiroyuki Narahara, Shingo Ishiguro, Takahiro Suzuki, and Toru Otani

Departments of Cancer Epidemiology [I. A., H. I., T. S.], Mass Screening [T. I.], Gastroenterology [I. K., H. N., T. O.], and Pathology [S. I.], Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka 537-8511, Japan

Abstract

To determine whether the colonic epithelial proliferation rate is useful as a marker for colorectal cancer, we measured the Ki-67 labeling index (LI) in normal-appearing mucosa from the sigmoid and ascending colon in patients with two or more tumors (early cancers, which are defined as tumors the depth of invasion of which is limited to mucosal layer or submucosal layer, adenomas, or both). The association of baseline LI with the risk of development of colon tumors 2 years after endoscopic removal was assessed by cohort analysis. The presence of two or more tumors was defined as occurrence. One hundred and six specimens from the sigmoid colon and 130 from the ascending colon from 246 subjects (203 males and 43 females) were used for analysis. The patients with higher upper-third LI in the normal-appearing mucosa in the sigmoid colon, but not in the ascending colon, had significantly more tumors at follow-up colonoscopy 2 years later (risk ratio, 3.6; 95% confidence interval, 1.2–10.6). Moreover, multivariate analysis showed that it was an independent factor. We concluded that the higher upper-third Ki-67 LI of normal-appearing mucosa in the sigmoid colon indicates a high risk for colorectal cancer.

Introduction

Colorectal cancer is one of the most common cancers in Western countries (1). In Japan, incidence of this cancer has rapidly increased, and this tendency is likely to continue (2). Colorectal epithelial proliferation is thought to be used as a biomarker for prevention of colorectal cancer (3), because epithelial proliferation is increased in persons who have or are at risk for colorectal neoplasms (4–7). However, the ability of this proliferation measured to predict future adenoma or cancer is not clear.

Several techniques, such as tritiated thymidine autoradiography, bromodeoxyuridine incorporation, Ki-67 immunohistochemistry, and crypt cell production rate, were used for the evaluation of cell proliferation. Ki-67 immunohistochemistry is one of the most widely available methods for measuring cell proliferation. Ki-67 antibody reacts with a nuclear antigen present in the G1, S, and G2 phases and mitosis but is absent in the G0 phase. Although Ki-67 immunohistochemistry developed first needed frozen sections (8), recently developed Ki-67 immunohistochemistry in formalin-fixed and paraffin-embedded tissues can be used as a reliable marker of the cell proliferation activity in both normal and neoplastic colonic epithelium (9–11). The Ki-67 LI is also a valuable prognostic indicator in several types of neoplasm (12–15).

In the present study, to determine whether the colonic epithelial proliferation rate can be used as an indicator of colorectal cancer risk, we measured the epithelial proliferation rate of normal-appearing colonic mucosa with the Ki-67 LI of the high-risk patients for colorectal cancer. We measured baseline LI and used cross-sectional analysis to assess its association with such factors as sex, age, diet, and lifestyle habits and the baseline colonoscopic findings. We also used cohort analysis to assess the association of baseline LI and the presence of two or more colorectal tumors after 2 years.

Materials and Methods

Study Participants. The subjects of the study were patients 40 to 65 years of age who had two or more histologically confirmed tumors [early cancers, which are defined as tumors the depth of invasion of which are limited to mucosal layer or submucosal layer (16), adenomas, or both] and were considered to be at high risk for colorectal cancer (17, 18). The study was approved by the Ethics Committee of Osaka Medical Center for Cancer and Cardiovascular Diseases (Osaka, Japan) in March 1993 and was started in June 1993. All of the subjects underwent total colonoscopy (baseline colonoscopy), and all of the polyps were resected endoscopically. Follow-up colonoscopy was performed at 2 years later. Biopsies were taken if any polyps were found at follow-up colonoscopy. Nakashima et al. (19) found 1.05 ± 0.08 neoplasms at surveillance colonoscopy after the previous polypectomy (mean duration was 8.73 months). This finding suggested that a single tumor might be missed sometimes at baseline colonoscopy. Therefore, the presence of two or more tumors at follow-up colonoscopy was defined as occurrence in this study.

A total of 246 persons (203 males and 43 females) were eligible for the present study.

Received 12/20/00; revised 5/17/01; accepted 6/25/01.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

1 Supported by a grant-in-aid for the Second-Term Comprehensive 10-Year Strategy for Cancer Control from the Ministry of Health and Welfare, Japan.

2 To whom requests for reprints should be addressed, at Department of Cancer Epidemiology, Research Institute, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Higashinari-ku, Nakamichi, Osaka 537-8511, Japan.

3 I. A. is an awardee of the Research Resident Fellowship from the Foundation for Promotion of Cancer Research in Japan.

4 The abbreviations used are: LI, labeling index; BMI, body mass index.
Measuring the Colonic Mucosal Cell Proliferation Rate. To measure the colonic cell proliferation rate at baseline colonoscopy, two biopsy specimens were obtained with a biopsy forceps 6 mm in diameter when opening the cups (FB-25U: Olympus, Tokyo, Japan), one from normal-appearing ascending colon mucosa (about 1 cm from ileocecal valve) and one from sigmoid colon mucosa (about 20 cm from the anal verge). Written informed consent was obtained before biopsy of normal-appearing mucosa. Before colonoscopy, the patients drank oral lavage isotonic solution of magnesium citrate (Magcokal P; Horii, Osaka, Japan). All of the patients finished the examination by early afternoon (between 10 a.m. and 2 p.m.). Biopsy specimens from the ascending colon and the sigmoid colon were immediately spread flat on paper, fixed in 10% neutral formalin, embedded in paraffin, and cut into 3-μm thick sections. Paraffin-embedded sections were mounted on polylysine-coated slides. To retrieve antigens, dewaxed paraffin slides were placed in jars filled with the citrate buffer (pH 6.0; 10 μmol) and incubated four times for 5 min at 500 W in a household microwave oven. The slides were then briefly washed with Tris-buffered saline and immunostained according to the standard protocol (20) with rabbit antimouse Ki-67 antigen (diluted 1:100 with PBS; DAKO Corp., Tokyo, Japan) as a primary antibody. Specimens were regarded as valid for analysis if at least five full longitudinal crypt sections were of high quality and scorable. The average of scored crypts was 7.8 (median, 8; range, 5 to 12) in the sigmoid colon and 7.6 (median, 7; range, 5 to 11) in the ascending colon. For each crypt, the number and the position of cells/crypt column and of labeled cells along the crypt were counted and recorded. Each crypt was divided into three equal compartments, upper (surface), middle, and lower, and LIs were calculated for the entire crypt and for the upper, middle, and lower thirds. The whole-crypt LI was the total number of all of the labeled cells in each crypt divided by the total number of cells in each crypt and multiplied by 100. The LI of each compartment was the number of labeled cells in the compartment divided by the number of cells in the compartment and multiplied by 100. The microscopic slides were read at random by one of the four technicians in a blinded manner so that patients could not be identified. Each slide was read by one technician. The average scores were not significantly different among four technicians. The association between LI value and various factors was assessed respectively in the sigmoid colon and the ascending colon. To facilitate the analysis for risk ratio, the LIs were divided into tertiles, low, middle, and high.

Assessment of Lifestyle and Diet. Data were collected from all of the study participants concerning their age, sex, height, body weight, colonoscopic findings at baseline, family history of malignancy, smoking habits, drinking habits, stool habits, diet at baseline, and colonoscopic findings at 2-year follow-up. Data regarding diet were collected by recording method over 3 consecutive weekdays. The exclusive dietician interviewed each patient on the basis of the dietary records. The mean daily intake of nutrients was calculated with a computer and a program based on the Fourth Revision of the Standard Tables of Food Composition in Japan (21), except for dietary fiber, which was based on a table (22) developed from the follow-up results of the Fourth Revision of the Standard Tables of Food Composition in Japan, Dietary Fiber (23).

Statistical Analysis. The t test was used to determine the significance of differences between two independent groups, and analysis of covariance was used to determine the differences among more than two independent groups and to investigate the relationship between LIs and the characteristics, lifestyle, or dietary nutrients at baseline. To facilitate the analysis of dietary intake, we divided subjects into two groups by the median value of each crude nutrient intake or nutrient density. Ps less than 0.05 were defined as significance.

The logistic regression model was used to analyze the relationship between LIs and the risk of development of tumors 2 years later. Possible risk factors for the occurrence of tumor at 2 years after entry to the study were investigated. A logistic model was used to analyze the risk ratio and 95% confidence interval of the number of tumors at baseline, the maximum size of tumor at baseline, baseline LI in the upper third, and whole crypt in the sigmoid colon and the ascending colon. Age was treated as a continuous variable and sex as a categorical variable. The number of tumors at baseline was divided into five categories: two, three, four, five, and six or more tumors. Tumors were also divided into two groups: those with a maximum size less than 9 mm and those with a maximum size of 9 mm or more. To confirm the independence of each LI, we included age and the number of tumors at baseline as continuous variables and gender as a categorical variable, because the number of tumors at baseline was considered a useful variable for the occurrence of tumors 2 years later (24).

Results

Relation to Lifestyle and Diet. A total of 106 specimens from the sigmoid colon and 130 specimens from the ascending colon from 246 participants could be used for analysis. Other specimens could not be used because full and scorable longitudinal crypts could not be obtained. The LIs in the sigmoid colon and the ascending colon were positively significantly correlated in 78 patients in whom LIs could be determined in both the sigmoid colon and ascending colon (whole crypt, \( r = 0.5, P < 0.01 \); upper third, \( r = 0.3, P < 0.01 \); middle third, \( r = 0.4, P < 0.01 \); lower third, \( r = 0.5, P < 0.01 \)). The LIs in the whole crypt and in the three compartments of the ascending colon were significantly higher than those of the sigmoid colon [ascending colon versus sigmoid colon (mean \( ± SD \); whole crypt, 23.6 ± 9.3 versus 17.2 ± 8.7; upper third, 4.2 ± 4.1 versus 1.8 ± 3.6; middle third, 28.4 ± 12.1 versus 15.7 ± 10.3; lower third, 36.5 ± 14.1 versus 28.5 ± 12.8; all of the LIs, \( P < 0.01 \)].

The mean LIs of the whole crypt and the upper third of the crypt in the sigmoid colon and the ascending colon according to patients’ characteristics are summarized in Table 1. Patients with a higher BMI had higher LIs than did the patients with a lower BMI. In particular, upper-third LIs in the ascending colon were significantly higher. Upper-third LIs in the sigmoid colon were higher in patients with watery or diarrheal stool than in patients with formed stool. This relation was also observed in the ascending colon but was not significant. LIs associated with dietary intake are shown according to the median crude nutrient intake, and the median of nutrient density of males are shown in Table 2. For females, similar results were obtained. Unexpectedly, male patients who had higher energy intake had significantly lower LIs in the sigmoid colon. Female patients with higher energy intake also had significantly lower LIs in the ascending colon. Assessment of LIs and crude nutrient intake showed that upper-third LIs in the sigmoid colon were significantly higher in patients with lower intake of total protein and of carbohydrates than in those with higher intake. Whole-crypt LIs in the sigmoid colon were significantly higher in patients with lower intake of carbohydrates, dietary fiber, and insoluble dietary fiber than in those with higher intake.
appearing mucosa in the sigmoid colon was an independent analysis revealed that the LI of the upper third of normal-used as an indicator of colorectal cancer risk. Multivariate whether the LI of normal-appearing colonic mucosa could be relation, which was not significant, was observed. The upper-third and whole-crypt LIs in the occurrence. All of the early cancers were found in patients with patients had no occurrence of tumors and 76 patients had 241 subjects who underwent follow-up colonoscopy, not undergo follow-up colonoscopy 2 years later. Of the re-
cancer at baseline in men or women. Although previous studies
carefully because these results could have occurred by chance. first to show a relationship between colorectal cell proliferation ascending colon and the sigmoid colon, respectively. This is the cancers (27–30), were correlated with the upper-third LI in the
diarrheal stool, which are possible risk factors for colorectal not), and dietary factors. We found that the BMI and watery or
colorectal cancer, such as age, sex, family history of colon
gate the relationship between Ki-67 LI and risk factors for
factor predicting the occurrence of tumors 2 years later. For other types of malignancy, the Ki-67 LI is a valuable prognostic indicator (12–15), and in the colon, cell proliferation of adenoma also has prognostic value (25). Bostick et al. (26) have also shown with cross-sectional analysis that the cell proliferation rate is positively correlated with the recurrence of polyp. Our prospective study is the first to show that the Ki-67 LI in normal-appearing colonic mucosa can predict the occurrence of tumors 2 years later.
At first, we performed a cross-sectional study to investigate the relationship between Ki-67 LI and risk factors for colorectal cancer, such as age, sex, family history of colon cancer, specific tumor characteristics (number, size, cancer or not), and dietary factors. We found that the BMI and watery or diarrheal stool, which are possible risk factors for colorectal cancers (27–30), were correlated with the upper-third LI in the ascending colon and the sigmoid colon, respectively. This is the first to show a relationship between colorectal cell proliferation rate and BMI or stool. However, we should take up these results carefully because these results could have occurred by chance. Additional studies would be required to confirm our results. In contrast, the LI was not correlated with sex, age, family history, number of tumors, size of tumors, or the presence or absence of cancer at baseline in men or women. Although previous studies

| Table 1 | Upper third and total LIs in the sigmoid and ascending colon according to characteristics at baseline |
|---------|-------------------------------------------------|-------------------------------------------------|---------|-------------------------------------------------|-------------------------------------------------|
|         | Sigmoid colon                                   | Ascending colon                                 |
|         | N      | Upper third | P   | Whole crypt | P               | N      | Upper third | P               | Whole crypt | P               |
| Age (median, year) |   |           |     |            |                 |       |           |     |            |                 |       |           |     |            |                 |
| Younger (less than 56) | 48 | 1.3 ± 1.8 | 17.1 ± 7.8 | 61 | 4.0 ± 3.9 | 21.2 ± 10.2 | 58 | 1.9 ± 4.1 | 0.28 | 17.3 ± 9.2 | 0.93 | 69 | 3.8 ± 4.3 | 0.85 | 22.4 ± 10.3 | 0.51 |
| Older   |       |           |     |            |                 |       |           |     |            |                 |       |           |     |            |                 |
| Sex     |       |           |     |            |                 |       |           |     |            |                 |       |           |     |            |                 |
| Female  | 19 | 1.2 ± 2.1 | 14.1 ± 7.9 | 21 | 4.4 ± 5.2 | 20.5 ± 9.8 | 87 | 1.7 ± 3.5 | 0.43 | 17.9 ± 8.6 | 0.08 | 109 | 3.8 ± 3.9 | 0.64 | 22.1 ± 10.3 | 0.51 |
| Male    |       |           |     |            |                 |       |           |     |            |                 |       |           |     |            |                 |
| Family history of malignancy | No | 39 | 1.4 ± 2.5 | 16.7 ± 8.6 | 45 | 3.9 ± 4.1 | 20.9 ± 10.8 | Yes | 52 | 1.0 ± 1.8 | 0.36 | 16.7 ± 8.1 | 0.10 | 68 | 3.7 ± 4.1 | 0.74 | 21.9 ± 10.7 | 0.63 |
| BMI (median) | Lower (less than 23.7) | 49 | 1.6 ± 3.2 | 16.8 ± 8.1 | 58 | 3.0 ± 2.8 | 21.1 ± 9.7 | Higher | 57 | 1.7 ± 3.4 | 0.88 | 17.5 ± 9.0 | 0.69 | 72 | 4.6 ± 4.8 | 0.83 | 22.4 ± 10.6 | 0.47 |
| Stool frequency | ≤1/day | 83 | 1.7 ± 3.0 | 16.6 ± 8.3 | 93 | 4.1 ± 4.3 | 22.8 ± 10.4 | >1/day | 23 | 1.3 ± 4.1 | 0.69 | 19.4 ± 9.1 | 0.20 | 37 | 3.4 ± 3.7 | 0.35 | 19.4 ± 9.4 | 0.08 |
| State of stool | Formed stool | 91 | 1.2 ± 2.2 | 16.6 ± 8.3 | 110 | 3.7 ± 4.1 | 21.3 ± 9.9 | Watery or diarrheal stool | 15 | 3.9 ± 6.6 | 0.01 | 19.1 ± 11.0 | 0.46 | 17 | 5.4 ± 3.8 | 0.10 | 27.4 ± 11.0 | 0.06 |
| Smoking | Never | 27 | 1.4 ± 2.4 | 14.3 ± 8.4 | 31 | 4.0 ± 4.9 | 22.6 ± 11.1 | Ever | 28 | 1.7 ± 3.7 | 15.8 ± 8.5 | 37 | 4.1 ± 3.9 | 20.4 ± 10.6 |
| Alcohol | No | 20 | 2.2 ± 4.5 | 15.9 ± 9.3 | 19 | 3.5 ± 5.1 | 21.9 ± 11.7 | Yes | 65 | 1.5 ± 3.0 | 0.52 | 16.4 ± 8.1 | 0.83 | 91 | 3.5 ± 3.5 | 0.99 | 21.7 ± 10.1 | 0.95 |
| No. of neoplasm at baseline | 2 | 20 | 2.9 ± 4.5 | 18.5 ± 10.2 | 23 | 4.4 ± 3.3 | 22.8 ± 9.2 | 3 | 21 | 1.0 ± 2.0 | 14.3 ± 8.6 | 24 | 3.4 ± 3.7 | 18.4 ± 11.8 |
|         | 4 | 15 | 1.0 ± 1.8 | 18.2 ± 8.7 | 21 | 4.5 ± 5.8 | 23.9 ± 12.9 | 5 | 13 | 1.5 ± 2.8 | 16.2 ± 5.6 | 15 | 4.6 ± 4.1 | 22.5 ± 8.6 |
|         | 6 or more | 37 | 1.6 ± 3.6 | 0.38 | 18.1 ± 8.4 | 0.64 | 47 | 3.3 ± 3.8 | 0.45 | 22.0 ± 8.9 | 0.71 |
| Maximum size of neoplasm at baseline | <9 mm | 47 | 1.4 ± 2.2 | 16.4 ± 8.0 | 62 | 4.4 ± 4.5 | 21.3 ± 10.4 | ≥9 mm | 59 | 1.8 ± 3.9 | 0.53 | 17.8 ± 9.0 | 0.38 | 68 | 3.4 ± 3.6 | 0.19 | 22.4 ± 10.1 | 0.56 |
| Early cancer at baseline | No | 67 | 1.7 ± 3.7 | 17.9 ± 9.0 | 87 | 3.6 ± 3.8 | 22.4 ± 9.9 | Yes | 39 | 1.6 ± 2.4 | 0.90 | 16.0 ± 7.7 | 0.29 | 43 | 4.4 ± 4.6 | 0.28 | 20.8 ± 10.9 | 0.40 |

**Discussion**

In our cross-sectional study and cohort study, we investigated whether the LI of normal-appearing colonic mucosa could be used as an indicator of colorectal cancer risk. Multivariate analysis revealed that the LI of the upper third of normal-appearing mucosa in the sigmoid colon was an independent factor predicting the occurrence of tumors 2 years later. For other types of malignancy, the Ki-67 LI is a valuable prognostic indicator (12–15), and in the colon, cell proliferation of adenoma also has prognostic value (25). Bostick et al. (26) have also shown with cross-sectional analysis that the cell proliferation rate is positively correlated with the recurrence of polyp. Our prospective study is the first to show that the Ki-67 LI in normal-appearing colonic mucosa can predict the occurrence of tumors 2 years later.

At first, we performed a cross-sectional study to investigate the relationship between Ki-67 LI and risk factors for colorectal cancer, such as age, sex, family history of colon cancer, specific tumor characteristics (number, size, cancer or not), and dietary factors. We found that the BMI and watery or diarrheal stool, which are possible risk factors for colorectal cancers (27–30), were correlated with the upper-third LI in the ascending colon and the sigmoid colon, respectively. This is the first to show a relationship between colorectal cell proliferation rate and BMI or stool. However, we should take up these results carefully because these results could have occurred by chance. Additional studies would be required to confirm our results. In contrast, the LI was not correlated with sex, age, family history, number of tumors, size of tumors, or the presence or absence of cancer at baseline in men or women. Although previous studies
have shown that the risk of colon adenoma or cancer was positively correlated with such dietary factors as total energy intake and the consumption of fat and red meat was negatively associated with the consumption of fruit and vegetables, dietary fiber, and calcium, we found, contrary to our expectations, that LIs were lower in both men and women with higher energy intake. Therefore, the relationship we observed was not consistent with previous reports.

The reason for this discrepancy is unclear. High-energy intake, especially high-fat intake, is thought to be a major risk factor for colon cancer. However, a recent study (31) of persons of Japanese descent living in Hawaii has shown that colon cancer risk is affected by both dietary and genetic factors. We speculated that in the Japanese, high-energy intake or high-fat intake do not necessarily increase the risk of colon cancer. Speculated that in the Japanese, high-energy intake or high-fat intake is thought to be a major risk factor for colon cancer, but no significant data were recognized in relation to LI. Naito et al. (33) have reported that persons with higher energy intake had higher levels of physical activity, which are thought to decrease the risk of colon cancer (27, 34). Therefore, physical activity might have acted as a confounding variable. In our study, we did not evaluate physical activity, so we could not determine the relationship of physical activity levels to energy intake. However, if subjects with higher energy intake had higher levels of physical activity, our finding that higher energy intake was correlated with lower LI would be consistent with findings of previous studies.

Another possible explanation for the correlation of lower LI with higher energy intake can be considered. Because our participants might have received information on the relationship between diet and colon neoplasms before their dietary habits changed their daily meals, although we instructed them not to change their diet, the presence of endoscopic treatment, they might have changed their daily meals, although we instructed them not to change their ordinary menu. Anyway, our cross-sectional study is the first report in Japanese subjects to use findings of total colonoscopy and dietary data recorded over 3 consecutive weekdays.

Because we could follow up almost all of the subjects in our cohort study, we could analyze the risk ratio of the occurrence of tumors after 2 years. We found that higher upper-third LIs in the sigmoid colon and higher whole-crypt LIs in the sigmoid colon could predict occurrence of tumors and that a higher upper-third LI in the sigmoid colon was an independent factor, as was the number of tumors at baseline. Recently, Sandler et al. (35) reported the association between LIs in rectum and colorectal neoplasm. The study design

### Table 2 LIs according to median nutrient intake in males

<table>
<thead>
<tr>
<th>Nutrient Density</th>
<th>Sigmoid colon</th>
<th>Ascending colon</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Upper third</td>
</tr>
<tr>
<td><strong>By crude nutrient intakes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total energy (kcal/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2136</td>
<td>43</td>
<td>2.5 ± 4.6</td>
</tr>
<tr>
<td>≥2136</td>
<td>44</td>
<td>0.9 ± 1.4</td>
</tr>
<tr>
<td>Total protein (g/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;84.9</td>
<td>42</td>
<td>2.6 ± 4.7</td>
</tr>
<tr>
<td>≥84.9</td>
<td>45</td>
<td>0.9 ± 1.4</td>
</tr>
<tr>
<td>Total lipid (g/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;52.4</td>
<td>44</td>
<td>2.0 ± 3.6</td>
</tr>
<tr>
<td>≥52.4</td>
<td>43</td>
<td>1.4 ± 3.3</td>
</tr>
<tr>
<td>Carbohydrates (g/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;272.8</td>
<td>49</td>
<td>2.5 ± 4.3</td>
</tr>
<tr>
<td>≥272.8</td>
<td>38</td>
<td>0.7 ± 1.3</td>
</tr>
<tr>
<td>Dietary fiber (g/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;14.8</td>
<td>42</td>
<td>2.2 ± 4.4</td>
</tr>
<tr>
<td>≥14.8</td>
<td>45</td>
<td>1.2 ± 2.1</td>
</tr>
<tr>
<td>Insoluble dietary fiber (g/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;11.5</td>
<td>44</td>
<td>2.1 ± 4.4</td>
</tr>
<tr>
<td>≥11.5</td>
<td>43</td>
<td>1.3 ± 2.2</td>
</tr>
</tbody>
</table>

(26, 29) have shown that the risk of colon adenoma or cancer was positively correlated with such dietary factors as total energy intake and the consumption of fat and red meat was negatively associated with the consumption of fruit and vegetables, dietary fiber, and calcium, we found, contrary to our expectations, that LIs were lower in both men and women with higher energy intake. Therefore, the relationship we observed was not consistent with previous reports.

The reason for this discrepancy is unclear. High-energy intake, especially high-fat intake, is thought to be a major risk factor for colon cancer. However, a recent study (31) of persons of Japanese descent living in Hawaii has shown that colon cancer risk is affected by both dietary and genetic factors. We speculated that in the Japanese, high-energy intake or high-fat intake do not necessarily increase the risk of colon cancer. According to Slattery et al. (32), various methods of analysis suggested that intake of individual sources of energy was not associated with colon cancer risk after total energy intake was taken into account. Their study population was American. Our study population was Japanese, and so we expected some association would be recognized. In this study, we analyzed not only by crude nutrient but also by nutrient density (each nutrient divided by total energy intake), but no significant data were recognized in relation to LI. Naito et al. (33) have reported that persons with higher energy intake had higher levels of physical activity, which are thought to decrease the risk of colon cancer (27, 34). Therefore, physical activity might have acted as a confounding variable. In our study, we did not evaluate physical activity, so we could not determine the relation of physical activity levels to energy intake. However, if subjects with higher energy intake had higher levels of physical activity, our finding that higher energy intake was correlated with lower LI would be consistent with findings of previous studies.

Another possible explanation for the correlation of lower LI with higher energy intake can be considered. Because our participants might have received information on the relationship between diet and colon neoplasms before their dietary habits changed their daily meals, although we instructed them not to change their ordinary menu. Anyway, our cross-sectional study is the first report in Japanese subjects to use findings of total colonoscopy and dietary data recorded over 3 consecutive weekdays.

Because we could follow up almost all of the subjects in our cohort study, we could analyze the risk ratio of the occurrence of tumors after 2 years. We found that higher upper-third LIs in the sigmoid colon and higher whole-crypt LIs in the sigmoid colon could predict occurrence of tumors and that a higher upper-third LI in the sigmoid colon was an independent factor, as was the number of tumors at baseline. Recently, Sandler et al. (35) reported the association between LIs in rectum and colorectal neoplasm. The study design
Nature of the study participants

We thank our four technicians, Miyako Sekido, Yuki Nakachi, Shouko Tatsumi, and Yui Yamasaki; our four dieticians, Tomiko Nakamura, Kazuko Kimura, Ruko Takeyama, and Sachayo Oku; and our three secretaries, Tomoko Saeki, Mayumi Nakaso, and Reiko Yamamoto for their data management and cooperation.

References


Colonic LI in High-Risk Patients for Colorectal Cancer


Evaluation of Epithelial Cell Proliferation Rate in Normal-appearing Colonic Mucosa as a High-Risk Marker for Colorectal Cancer

Ikuko Akedo, Hideki Ishikawa, Tatsuya Ioka, et al.


Updated version
Access the most recent version of this article at:
http://cebp.aacrjournals.org/content/10/9/925

Cited articles
This article cites 27 articles, 7 of which you can access for free at:
http://cebp.aacrjournals.org/content/10/9/925.full#ref-list-1

Citing articles
This article has been cited by 5 HighWire-hosted articles. Access the articles at:
http://cebp.aacrjournals.org/content/10/9/925.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.