Obesity, Weight Gain and Risk of Colon Adenomas in Japanese Men

Suminori Kono,[1,6] Koichi Handa,[2] Hitomi Hayabuchi,[3] Chikako Kiyohara,[1] Hisako Inoue,[1] Tomomi Marugame,[1] Sachiko Shinomiya,[1] Hiroaki Hamada,[4] Kazuya Onuma[4] and Hiroko Koga[5]

[1]*Department of Preventive Medicine, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582,* [2]*Fukuoka University School of Medicine, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180,* [3]*Fukuoka Women's University, 1-1-1 Kasumigaoka, Higashi-ku, Fukuoka 813-0003,* [4]*Self Defense Forces Fukuoka Hospital, 173-2 Kokura, Kasuga-shi, Fukuoka 816-0824 and* [5]*Self Defense Forces Kumamoto Hospital, 15-1 Higashihonmachi, Kumamoto 862-0901*

Obesity has been related to increased risk of colon cancer or adenomas, but the epidemiologic findings are not entirely consistent. We examined the relation of not only body mass index (BMI) but also waist-to-hip ratio (WHR) and weight gain to colon adenoma risk in men who received a preretirement health examination at the Japan Self Defense Forces (SDF) Fukuoka and Kumamoto Hospitals during the period from 1995 to 1996. In the series of 803 men at age 47–55 years, 189 cases of colon adenomas and 226 controls with normal total colonoscopy were identified. Weight at 10 years before was ascertained by referring to the recorded data. After allowance for hospital, rank in the SDF, smoking and alcohol use, weight gain over the past 10 years was significantly associated with increased risk of colon adenomas (odds ratio for ≥6 kg versus ≤–2 kg = 2.2; 95% confidence interval 1.0–4.8). High BMI and high WHR were each associated with increased risk, but only WHR was related to the risk independently of weight gain. In particular, weight gain accompanied with a high WHR was associated with a significant increase in the risk. Men with high physical activity tended to have lower risk. Associations with obesity-related variables and physical activity were not materially differential as regards the location and size of adenoma. The findings indicate that weight gain in middle age leading to abdominal obesity increases the risk of colon adenomas, and consequently of colon cancer.

Key words: Colon adenomas — Obesity — Waist-to-hip ratio — Physical activity

It has been suggested that obesity may confer increased risk of colon cancer, but the epidemiologic findings on the relation between obesity and colon cancer are not entirely consistent.[1, 2] Several studies have also addressed the relation of obesity to colon or colorectal adenomas,[3–11] a well-established precursor lesion of the large bowel.[12, 13] As compared with studies of colorectal cancer, studies of colorectal adenomas have methodological advantages in that bias related to weight loss in proximity to the diagnosis of cancer is avoided and that more recent conditions rather than those in the distant past are relevant to the occurrence of adenomas. Nonetheless, previous studies of colon or colorectal adenomas have reported inconsistent findings regarding obesity and adenoma risk. Most of these studies as well as those of colon cancer have used body mass index (BMI) as a measure of obesity. Few studies of adenomas examined the association with other aspects of obesity, such as waist-to-hip ratio (WHR)[6, 8, 9] and weight gain.[10, 11]

Using body weight recorded 10 years before, we examined the risk of colon adenomas in relation to past and current BMI, WHR, and weight gain over the past 10 years in middle-aged Japanese men. Because physical activity has consistently been shown to be associated with decreased risk of colon adenomas[5, 8, 9, 14, 15] as well as of colon cancer[16, 17] and because physical activity is closely associated with obesity, we also investigated the relation between recreational physical activity and colon adenomas.

SUBJECTS AND METHODS

Study subjects were male self-defense officials who received a preretirement health examination at the Self Defense Forces (SDF) Fukuoka Hospital from January 1995 to December 1996 and the SDF Kumamoto Hospital from May to December 1996. The preretirement health examination is a nationwide program offering a comprehensive medical examination for those retiring from the SDF, and these two hospitals cover the Kyushu region. Details of the health examination have been described

elsewhere.[6, 7, 14] Routine medical examinations included colonoscopy and blood biochemical measurements during a 5-day admission.

In the consecutive series of 803 men, 778 underwent total or partial colonoscopy. Excluded from the study were 41 men with a prior history of colectomy (n=3), colorectal polypectomy (n=36) or malignant neoplasms (n=4); there was no case with inflammatory bowel disease. Numbers of men according to the colonoscopic findings among 737 men were: normal 368, polyps 325, carcinoma 2 and other lesions 42. A total of 189 out of the 325 men with colorectal polyps were found to have histologically confirmed colon adenomas without *in situ* or invasive carcinoma; colon adenomas were defined as those located at a depth of more than 10 cm from the anus. Of the 368 men with normal findings, 230 received total colonoscopy. The present study used 189 cases of colon adenomas and 226 controls with normal total colonoscopy, excluding four controls whose waist and hip circumferences were not recorded. Adenomas located at a depth of 11–60 cm from the anus were defined as distal colon adenomas, and those at a depth of more than 60 cm were regarded as proximal colon adenomas. Numbers of cases with adenomas at the distal colon alone, proximal colon alone and both distal and proximal colon were 92, 72 and 25, respectively. Numbers of cases with an adenoma of <5 mm, ≥5 mm and unknown size (diameter of the largest adenoma) were 118, 66 and 5, respectively.

Height and body weight were recorded, and BMI, weight in kilograms divided by squared height in meters, was calculated. Waist and hip circumferences were measured in the horizontal plane at the level of the umbilicus and at the largest circumference around the buttocks, respectively, to obtain WHR as a measure of abdominal obesity. Body weight 10 years before was extracted from the record of biannual health check-up, which was kept individually and submitted to the ward at the time of the health examination. Record of the past body weight was not available for 15 men, and the self-reported weight was used as a substitute.

A self-administered questionnaire ascertained smoking habit, alcohol use, recreational exercise, dietary habits and other personal information with a supplementary interview for unanswered questions. Lifetime exposure to cigarette smoking was expressed as cigarette-years, the average number of cigarettes smoked per day multiplied by years of smoking. Alcohol intake was calculated for current alcohol drinkers based on consumption frequencies and amounts consumed per occasion of five different alcoholic beverages (*sake*, *shochu*, beer, spirits and wine) on average in the past year. Former alcohol drinkers were separated from lifelong nondrinkers. As for physical activity, subjects were first asked about the frequency of participation in recreational exercises and sports on average in the

past year using a closed-ended question (hardly, 1–2, 3–4 or 5–6 times per week and daily). If the participation was 1–2 times per week or more frequent, the type of regular exercise or sport and the time spent per occasion were ascertained by open-ended questions. Approximately 5% reported plural (more than one) regular activities of different intensities. In accordance with the published energy expenditure requirements in terms of metabolic equivalents (METs) for different physical activities,[18] reported types of exercise and sport were classified into light, moderate, heavy and very heavy activities. The time spent at recreational exercise was multiplied by the corresponding MET value (light 2, moderate 4, hard 6 and very hard 8) to yield an MET-hour score. In the whole group of subjects (n=803), the MET-hours were modestly correlated with serum HDL cholesterol levels (Spearman's rank correlation coefficient=0.13).

In statistical analysis, levels of obesity indices and MET-hours were categorized into four groups at the cutoff points of 30th, 60th and 90th percentiles in the distributions of cases and controls combined. Adjustment was made for hospital, rank in the SDF, cigarette smoking and alcohol use by logistic regression analysis. Age was not taken into account because the age range was limited (47–55 years) and 99% were at age 50–54 years. Cigarette smoking was categorized into 0, 1–399, 400–799 and ≥ 800 cigarette-years; alcohol use was classified into never, past and current use with a consumption of <30, 30–59 or ≥60 ml of alcohol per day; and rank of the SDF into low, middle and high ranks. Indicator variables were created for these covariates as well as obesity-related variables and MET-hours. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated from logistic regression coefficients and standard errors for the corresponding indicator variables. Trend of the association was assessed by the Wald statistic in logistic regression analysis, in which median values were assigned to categories of each factor. Interaction was statistically evaluated by the likelihood ratio test. Two-sided P values less than 0.05 were regarded as statistically significant. All statistical computations were done with PC-SAS version 6.04 (SAS Institute, Inc., Cary, NC).

RESULTS

Table I shows the association of obesity-related variables and physical activity with colon adenoma after adjustment for hospital, rank in the SDF, cigarette smoking and alcohol use. BMI at 10 years before colonoscopy was not materially related to colon adenomas. Weight gain over the past 10 years was significantly related to increased risk of colon adenomas, showing a progressive increase in the ORs with increasing levels of weight gain; as compared with those having lost weight, an approxi-

Table I. Adjusted Odds Ratios (OR)[a] and 95% Confidence Intervals (CI) of Colon Adenomas in Relation to Obesity-related Variables and Physical Activity

Variable[b]	No. of cases	No. of controls	Adjusted OR (95%CI)
Body mass index 10 years before			
<22.25	53	73	1.0
22.25–23.88	57	66	1.1 (0.7–1.9)
23.89–26.49	56	68	1.2 (0.7–2.0)
≥26.50	23	19	1.5 (0.7–3.1)
Trend[c]			$P=0.30$
Body mass index at examination			
<22.45	48	77	1.0
22.45–24.30	59	65	1.6 (0.9–2.7)
24.31–26.89	57	68	1.2 (0.7–2.1)
≥26.90	25	16	2.4 (1.1–5.1)
Trend[c]			$P=0.06$
Waist-to-hip ratio			
<0.873	41	81	1.0
0.873–0.907	65	62	2.2 (1.3–3.8)
0.908–0.956	61	62	1.8 (1.1–3.2)
≥0.957	22	21	2.0 (0.9–4.2)
Trend[c]			$P=0.03$
Weight gain (kg)			
≤−2	42	68	1.0
−1 to 1	62	77	1.6 (0.9–2.7)
2 to 5	62	64	1.8 (1.0–3.0)
≥6	23	17	2.2 (1.0–4.8)
Trend[c]			$P=0.02$
MET-hours per week			
<4	71	53	1.0
4–14	50	76	0.6 (0.3–1.0)
15–35	51	73	0.6 (0.4–1.1)
≥36	17	24	0.6 (0.3–1.3)
Trend[c]			$P=0.17$

a) Adjusted for hospital, rank, cigarette smoking and alcohol use.
b) Categorized at the 30th, 60th, and 90th percentiles in cases and controls combined.
c) Median values in the categories were assigned to the corresponding levels.

mately two-fold increase in the OR was noted among those having gained 6 kg or more. Current BMI and WHR were also associated with increased risk of colon adenomas, but the ORs did not increase linearly with increasing levels of BMI or WHR. Physical activity in terms of MET-hours was weakly, inversely associated with colon adenomas. Men in the three groups of 4 MET-hours or greater showed equally decreased ORs as compared with those at the lowest 30%.

Weight gain over the past 10 years was moderately correlated with current BMI (Pearson's correlation coefficient $r=0.45$) and WHR ($r=0.35$). Because current BMI and WHR were considered to be largely secondary to weight gain, we used residuals of the BMI and WHR from each linear regression on weight gain in order to examine the relation of current BMI and WHR to colon adenomas independently of weight gain. The residual BMI and WHR, as calculated by the Willett's method,[19] are quantities uncorrelated with weight gain. Table II shows adjusted ORs of colon adenomas according to levels of weight gain, residual WHR, and physical activity with mutual adjustment for these three variables. The relationship with the residual WHR was not much different from that for the unadjusted WHR, while associations with weight gain and physical activity were slightly attenuated. The residual BMI, when included in the model instead of the residual WHR, was no longer associated with adenoma risk; adjusted ORs (and 95%CI) for the lowest to highest levels were 1.0 (referent), 1.1 (0.6–1.8), 1.2 (0.7–2.0) and 1.4 (0.6–2.9), respectively.

Table II. Adjusted Odds Ratios (OR)[a] and 95% Confidence Intervals (CI) of Colon Adenomas in Relation to Weight Gain, Residual Waist-to-hip Ratio (WHR) and Physical Activity in Multivariate Analysis

Variable	Category by percentile[b]				Trend[c]
	≤30	31–60	61–90	>90	
Weight gain (kg)	1.0	1.4 (0.8–2.5)	1.6 (0.9–2.8)	1.8 (0.8–4.1)	$P=0.07$
Residual WHR[d]	1.0	2.1 (1.2–3.7)	1.5 (0.9–2.6)	2.1 (1.0–4.5)	$P=0.08$
MET-hours per week	1.0	0.6 (0.4–1.1)	0.7 (0.4–1.3)	0.7 (0.3–1.5)	$P=0.42$

a) Based on a logistic regression model including variables for hospital, rank, cigarette smoking, alcohol use and the listed three factors.
b) Based on the distributions of cases and controls combined.
c) Median values in the categories were assigned to the corresponding levels.
d) Residual from a linear regression on weight gain as calculated by Willett's method.

Table III. Adjusted Odds Ratios (OR)[a] of Colon Adenomas and 95% Confidence Intervals (CI) according to the Combination of Weight Gain and Waist-to-hip Ratio

Weight gain (kg)	Waist-to-hip ratio[b]	No. of cases	No. of controls	Adjusted OR (95%CI)
<2	<0.873	33	63	1.0
<2	≥0.873	71	82	1.7 (1.0–3.0)
≥2	<0.873	8	18	1.0 (0.4–2.7)
≥2	≥0.873	77	63	2.2 (1.2–3.9)

a) Adjusted for hospital, rank, cigarette smoking, alcohol use and MET-hours.
b) The cutoff point was the 30th percentile in the distribution of cases and controls combined.

Table IV. Adjusted Odds Ratios (OR)[a] and 95% Confidence Intervals (CI) of Colon Adenomas by Subsite and Size in Relation to Weight Gain, Waist-to-hip Ratio and Physical Activity

Variable	Subsite[b] or size of adenoma	Category by percentile[c]		
		31–60	61–90	91+
Weight gain (kg)	Distal	1.9 (1.0–3.6)	2.1 (1.1–4.0)	2.5 (1.0–6.1)
	Proximal	1.5 (0.7–2.9)	1.5 (0.8–3.0)	2.5 (1.0–6.3)
Waist-to-hip ratio	Distal	2.3 (1.2–4.4)	1.6 (0.8–3.1)	2.8 (1.2–6.3)
	Proximal	2.8 (1.4–5.6)	2.8 (1.4–5.7)	1.6 (0.5–4.5)
MET-hours per week	Distal	0.6 (0.3–1.1)	0.7 (0.4–1.2)	0.7 (0.3–1.6)
	Proximal	0.5 (0.2–0.9)	0.5 (0.3–0.9)	0.6 (0.3–1.6)
Weight gain (kg)	Small (<5 mm)	1.7 (0.9–3.2)	1.5 (0.8–2.9)	2.2 (0.9–5.3)
	Large (≥5 mm)	1.7 (0.7–3.8)	2.3 (1.0–5.3)	2.6 (0.9–8.0)
Waist-to-hip ratio	Small (<5 mm)	2.5 (1.3–4.8)	2.3 (1.2–4.4)	2.0 (0.8–4.8)
	Large (≥5 mm)	1.6 (0.8–3.4)	1.3 (0.6–2.8)	1.6 (0.6–4.8)
MET-hours per week	Small (<5 mm)	0.6 (0.3–1.0)	0.5 (0.3–0.9)	0.4 (0.2–1.1)
	Large (≥5 mm)	0.4 (0.2–0.9)	0.9 (0.4–1.8)	0.8 (0.3–2.2)

a) Adjusted for hospital, rank, cigarette smoking and alcohol use.
b) Cases with adenomas at both distal and proximal colon were included in each group.
c) Based on the distributions of cases and controls combined. Referent category was the lowest 30%.

We further examined the risk of colon adenomas in relation to the combination of weight gain and WHR categories (Table III). In this analysis, weight gain was dichotomously categorized at a 2-kg gain, and the 30th percentile was taken as a cutoff point of WHR, because the ORs associated with WHR were increased almost equally above that point, as seen above. Men having gained weight but without a high WHR showed no increase in the OR as compared with those with no weight gain and a low WHR. Weight gain with a high WHR was

significantly associated with more than two-fold increased risk. A high WHR without weight gain was also related to an increased risk, but the increase was not statistically significant (*P*=0.07). The interaction between weight gain and high WHR was not statistically significant (*P*=0.65).

Table IV shows associations with weight gain, WHR, and physical activity by subsite and size of adenoma. There was not much difference in the association with these factors either between distal and proximal colon adenomas or between small and large adenomas. An exception was that increased ORs associated with WHR tended to be more pronounced for small adenomas.

DISCUSSION

The present study demonstrated that weight gain over the past 10 years was related to increased risk of colon adenomas. This finding is in agreement with two previous studies of colorectal adenomas.[10, 11] One of these studies showed that weight gain in adulthood was positively associated with colorectal adenomas,[10] and the other reported that weight gain in the past 10 years, but not either in the past 5 years or in adulthood, was directly related to adenomas of the distal colon and rectum combined.[11] In the latter study, the relation between weight gain and adenoma risk was substantially attenuated when current BMI was included in a multiple logistic regression model.[11] In middle-aged and elderly persons, high BMI at present is mostly secondary to weight gain, as seen from a moderate correlation between the two variables in the present study. Thus, results from the multiple logistic regression used for mutual adjustment for current BMI and weight gain would be misleading. To avoid problems due to colinearity, we used residuals of BMI and WHR from their linear regression models in relation to weight gain. The current BMI uncorrelated with weight gain represents a sustained level of BMI, i.e., BMI at 10 years before in the present study. Thus ORs according to the residual BMI at present were essentially the same as ORs in relation to BMI at 10 years before.

A direct association between BMI and distal colon adenomas was found in prospective studies of men and women in the United States.[8, 9] While some case-control studies showed a positive association between BMI and colon or colorectal adenomas in men[6, 7] and in both sexes combined,[11] others did not find such an association in either men or women.[3, 5] Another study demonstrated an evident, positive association with BMI in females, but found no clear positive association in males.[4] Current BMI may have reflected weight gain and obesity level differently in different study populations.

WHR was not as strongly correlated with weight gain as BMI, and high WHR was found to be related to increased risk of colon adenomas independently of weight gain.

Although the interaction between weight gain and WHR, each categorized dichotomously, was not statistically significant, it is notable that men having gained weight with a high WHR showed a significant increase in adenoma risk whereas such men without a high WHR had no increased risk. These findings suggest that weight gain leading to abdominal obesity is particularly important in the development of colon tumor. Three studies previously addressed the relation between WHR and adenomas of the distal colon, and reported increased risk in relation to high WHR,[6, 8, 9] and independently of BMI in men.[6, 8] A positive association between WHR and colon cancer independent of BMI was also found in prospective studies of American men and women,[8, 20] but not in another prospective study of American women.[21]

The mechanism underlying the positive association with weight gain or obesity remains unknown. Excess energy intake necessarily leads to weight gain and obesity. Calorie restriction is known to inhibit the occurrence of colon cancer in rodents.[22] It was also shown in obese humans that calorie restriction caused a reduction in rectal cell proliferation, an intermediate marker of colon carcinogenesis.[23] Hyperinsulinemia or insulin resistance, which commonly occurs in association with abdominal obesity, is a possible mediator in the development of colon tumors.[24, 25] It has been shown recently that insulin promotes colon tumors[26] and the growth of colonic aberrant crypt foci in rats.[27]

Our findings on physical activities are consistent with current knowledge that physical activity is related to decreased risk of colon adenomas as well as colon cancer. Some studies reported that a protective association with physical activity was stronger for distal colon cancer than for proximal colon cancer,[8, 20, 28] whereas others showed a stronger, inverse association with proximal colon cancer,[29] an inverse association with right-sided colon cancer[30] and an inverse relation for both distal and proximal colon cancer.[31] Previous studies of colon adenomas have not addressed the relation to physical activity by location of colon. The present study found no material difference between proximal and distal colon adenomas as regards the association with physical activity. Further studies are needed regarding this issue.

It has also been suggested that obesity may be related to large adenomas of the colon, thereby promoting the growth of adenomas. Both BMI and WHR were associated with increased risk of large adenomas, defined as 10 mm or greater in diameter, but not with small adenomas in prospective studies of American men and women.[8, 9] In a recent case-control study of colorectal adenomas,[11] BMI and weight gain was more strongly related to large adenomas (10 mm or greater). In a previous study of male self-defense officials,[6] WHR was related primarily to increased risk of large adenomas (5 mm or greater) of the

sigmoid colon. The present study did not corroborate these previous findings. Because the majority of colon adenomas in the present study were less than 10 mm, we were unable to perform an analysis of adenomas of 10 mm or greater in size. Dividing adenoma size at 5 mm may be more subject to misclassification, which necessarily dilutes differential associations, if any, for small and large adenomas. More evidence is needed to draw a conclusion that obesity promotes the growth of adenomas.

The present study had methodological strengths. Selection bias can be ruled out because subjects unselectively underwent colonoscopy. Controls were those who had no pathological lesion as ascertained by total colonoscopy, and the present study avoided the contamination of controls with adenoma cases, which always occurs in sigmoidoscopy-based studies. We used recorded body weight at 10 years before, while previous studies relied on self-reported weight in the past. However, weaknesses also need to be clarified. Physical activity was ascertained on the basis of self-reported recreational activity alone. Although recall bias is impossible, physical activity may have been underestimated and suffered from misclassification. Thus, the reported association between physical activity and colon adenomas was probably underestimated. Dietary factors were not taken into account. Positive energy balance results in weight gain, and energy-dense nutrients and foods such as fat and refined sugar, which are suspected to increase colon cancer risk,[1, 2] may have confounded the relation of weight gain or WHR to colon adenomas. Detailed dietary data were not available in the present study. Yet, as seen from previous studies allowing for

foods and nutrients,[8, 9, 11] it is unlikely that the observed associations with obesity and physical activity can be totally ascribed to specific dietary factors. Finally, the study subjects were men serving in the SDF until retirement. They may differ from men in the general population in terms of physical activity and body build, and our findings may not be general. However, the BMI of the study subjects (mean=23.7) was comparable to that of average middle-aged Japanese men; the mean for men in their 50s was estimated to be 23.4 from the average height and body weight reported in the National Nutrition Survey in 1995.[32]

In conclusion, weight gain in middle age, especially accompanied with high WHR, was shown to be associated with increased risk of colon adenomas in a relatively thin, male population. These findings suggest that maintenance and preferably reduction of body weight in middle age are beneficial for the prevention of colon adenomas, and consequently of colon cancer.

REFERENCES

1) Potter, J. D., Slattery, M. L., Bostick, R. M. and Gapstur, S. M. Colon cancer: a review of the epidemiology. *Epidemiol. Rev.*, **15**, 499–545 (1993).
2) World Cancer Research Fund and American Institute for Cancer Research. "Food, Nutrition and the Prevention of Cancer: a Global Perspective," pp. 216–251 (1997). American Institute for Cancer Research, Washington, DC.
3) Mannes, G. A., Maier, A., Thieme, C., Wiebecke, B. and Paumgartner, G. Relation between the frequency of colorectal adenoma and the serum cholesterol level. *N. Engl. J. Med.*, **315**, 1634–1638 (1986).
4) Neugut, A. I., Lee, W. C., Garbowski, G. C., Waye, J. D., Forde, K. A., Treat, M. R. and Fenoglio-Preiser, C. Obesity and colorectal adenomatous polyps. *J. Natl. Cancer Inst.*, **83**, 359–361 (1991).
5) Little, J., Logan, R. F., Hawtin, P. G., Hardcastle, J. D. and Turner, I. D. Colorectal adenomas and energy intake, body size and physical activity: a case-control study of subjects participating in the Nottingham faecal occult blood screening programme. *Br. J. Cancer*, **67**, 172–176 (1993).
6) Shinchi, K., Kono, S., Honjo, S., Todoroki, I., Sakurai, Y., Imanishi, K., Nishikawa, H., Ogawa, S., Katsurada, M. and Hirohata, T. Obesity and adenomatous polyps of the sigmoid colon. *Jpn. J. Cancer Res.*, **85**, 479–484 (1994).
7) Honjo, S., Kono, S., Shinchi, K., Wakabayashi, K., Todoroki, I., Sakurai, Y., Imanishi, K., Nishikawa, H., Ogawa, S. and Katsurada, M. The relation of smoking, alcohol use and obesity to risk of sigmoid colon and rectal adenomas. *Jpn. J. Cancer Res.*, **86**, 1019–1026 (1995).
8) Giovannucci, E., Ascherio, A., Rimm, E. B., Colditz, G. A., Stampfer, M. J. and Willett, W. C. Physical activity, obesity, and risk for colon cancer and adenoma in men. *Ann. Intern. Med.*, **122**, 327–334 (1995).
9) Giovannucci, E., Colditz, G. A., Stampfer, M. J. and Willett, W. C. Physical activity, obesity, and risk of colorectal adenoma in women (United States). *Cancer Causes Control*, **7**, 253–263 (1996).
10) Lubin, F., Rozen, P., Arieli, B., Farbstein, M., Knaani, Y., Bat, L. and Farbstein, H. Nutritional and lifestyle habits and water-fiber interaction in colorectal adenoma etiology.

Cancer Epidemiol. Biomarkers Prev., **6**, 79–85 (1997).

11) Bird, C. L., Frankl, H. D., Lee, E. R. and Haile, R. W. Obesity, weight gain, large weight changes, and adenomatous polyps of the left colon and rectum. *Am. J. Epidemiol.*, **147**, 670–680 (1998).

12) Hill, M. J., Morson, B. C. and Bussey, H. J. Aetiology of adenoma—carcinoma sequence in large bowel. *Lancet*, **i**, 245–247 (1978).

13) Neugut, A. I., Jacobson, J. S. and DeVivo, I. Epidemiology of colorectal adenomatous polyps. *Cancer Epidemiol. Biomarkers Prev.*, **2**, 159–176 (1993).

14) Kono, S., Shinchi, K., Ikeda, N., Yanai, F. and Imanishi, K. Physical activity, dietary habits and adenomatous polyps of the sigmoid colon: a study of self-defense officials in Japan. *J. Clin. Epidemiol.*, **44**, 1255–1261 (1991).

15) Neugut, A. I., Terry, M. B., Hocking, G., Mosca, L., Garbowski, G. C., Forde, K. A., Treat, M. R. and Waye, J. Leisure and occupational physical activity and risk of colorectal adenomatous polyps. *Int. J. Cancer*, **68**, 744–748 (1996).

16) Macfarlane, G. J. and Lowenfels, A. B. Physical activity and colon cancer. *Eur. J. Cancer Prev.*, **3**, 393–398 (1994).

17) Colditz, G. A., Cannuscio, C. C. and Frazier, A. L. Physical activity and reduced risk of colon cancer: implications for prevention. *Cancer Causes Control*, **8**, 649–667 (1997).

18) Ainsworth, B. E., Haskell, W. L., Leon, A. S., Jacobs, D. R., Jr., Montoye, H. J., Sallis, J. F. and Paffenbarger, R. S., Jr. Compendium of physical activities: classification of energy costs of human physical activities. *Med. Sci. Sports Exerc.*, **25**, 71–80 (1993).

19) Willett, W. "Nutritional Epidemiology," pp. 245–271 (1990). Oxford University Press, Oxford.

20) Martinez, M. E., Giovannucci, E., Spiegelman, D., Hunter, D. J., Willett, W. C. and Colditz, G. A. Leisure-time physical activity, body size, and colon cancer in women. Nurses' Health Study Research Group. *J. Natl. Cancer Inst.*, **89**, 948–955 (1997).

21) Bostick, R. M., Potter, J. D., Kushi, L. H., Sellers, T. A., Steinmetz, K. A., McKenzie, D. R., Gapstur, S. M. and Folsom, A. R. Sugar, meat, and fat intake, and non-dietary risk factors for colon cancer incidence in Iowa women (United States). *Cancer Causes Control*, **5**, 38–52 (1994).

22) Macrae, F. A. Fat and calories in colon and breast cancer: from animal studies to controlled clinical trials. *Prev. Med.*, **22**, 750–766 (1993).

23) Steinbach, G., Heymsfield, S., Olansen, N. E., Tighe, A. and Holt, P. R. Effect of caloric restriction on colonic proliferation in obese persons: implications for colon cancer prevention. *Cancer Res.*, **54**, 1194–1197 (1994).

24) McKeown-Eyssen, G. Epidemiology of colorectal cancer revisited: are serum triglycerides and/or plasma glucose associated with risk? *Cancer Epidemiol. Biomarkers Prev.*, **3**, 687–695 (1994).

25) Giovannucci, E. Insulin and colon cancer. *Cancer Causes Control*, **6**, 164–179 (1995).

26) Tran, T. T., Medline, A. and Bruce, W. R. Insulin promotion of colon tumors in rats. *Cancer Epidemiol. Biomarkers Prev.*, **5**, 1013–1015 (1996).

27) Corpet, D. E., Jacquinet, C., Peiffer, G. and Tache, S. Insulin injections promote the growth of aberrant crypt foci in the colon of rats. *Nutr. Cancer*, **27**, 316–320 (1997).

28) Gerhardsson de Verdier, M., Steineck, G., Hagman, U., Rieger, A. and Norell, S. E. Physical activity and colon cancer: a case-referent study in Stockholm. *Int. J. Cancer*, **46**, 985–989 (1990).

29) Thune, I. and Lund, E. Physical activity and risk of colorectal cancer in men and women. *Br. J. Cancer*, **73**, 1134–1140 (1996).

30) Longnecker, M. P., Gerhardsson le Verdier, M., Frumkin, H. and Carpenter, C. A case-control study of physical activity in relation to risk of cancer of the right colon and rectum in men. *Int. J. Epidemiol.*, **24**, 42–50 (1995).

31) Slattery, M. L., Potter, J., Caan, B., Edwards, S., Coates, A., Ma, K. N. and Berry, T. D. Energy balance and colon cancer—beyond physical activity. *Cancer Res.*, **57**, 75–80 (1997).

32) Japan Ministry of Health and Welfare. "Annual Report of the National Nutrition Survey in 1995," p. 109 (1997). Dai-ichi-shuppan, Tokyo.