Effect of Caloric Restriction on Colonic Proliferation in Obese Persons: Implications for Colon Cancer Prevention

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ABSTRACT

Dietary intervention to prevent colon cancer is a major health issue. At present it is not clear which dietary factors modify colon cancer risk. Caloric restriction reduces the incidence of many spontaneous and carcinogen-induced tumors in rodents, but its role in human carcinogenesis is unknown. The relationships of body mass index (BMI), body composition, and resting metabolic rate (RMR) to colon cancer risk are also undefined. In this study involving obese persons, we measured the effect of reducing caloric intake on rectal cell proliferation, a biomarker in colon carcinogenesis, and studied the relation of BMI, body composition, and RMR to rectal cell proliferation. Colonic cell proliferation was measured in rectal biopsies from persons weighing more than 130% of ideal body weight. Follow-up biopsies were performed in patients who enrolled in and completed a 16-week behavior modification weight-reduction program in which caloric intake was reduced. Baseline measurements included body composition by total body electrical conductance, RMR, and BMI. Rectal biopsies were processed for autoradiography following incubation with $[^3H]$thymidine. Epithelial proliferation measurements were evaluable in 35 persons at baseline and in 8 persons before and after caloric restriction. Before caloric restriction, mean (± SD) BMI was 38 ± 4 kg/m² and percentage of body fat 41 ± 2%. Subjects reduced their caloric intake by a mean of 34 ± 4% and their weight by 8.6 ± 1%. Caloric restriction resulted in a 39% reduction in whole-crypt labeling index ($P < 0.001$) and a 57% reduction in upper crypt labeling index ($P < 0.05$) without reduction in crypt depth. Labeling index was unrelated to BMI, RMR, or body composition. We conclude that caloric restriction reduced rectal cell proliferation measurements—intermediate biomarkers related to colon carcinogenesis. BMI, RMR, and body composition were unrelated to colonic proliferation. Caloric restriction may have a role in colon cancer prevention.

INTRODUCTION

Caloric restriction consistently reduces the incidence of spontaneous and carcinogen-induced tumors (1–6), including colon tumors (7–10), in rodents. The consequences of reduced dietary caloric intake on human colon carcinogenesis is, however, still unknown. Epidemiological data, which point to a relationship between diet and colon cancer, suggest a positive correlation of dietary fat and caloric intake with colon cancer risk (11–16). More precise experimental data on dietary factors that influence colon carcinogenesis in humans would be important in designing preventive dietary strategies.

Diet intervention studies that involve caloric restriction and have colon tumors as an endpoint are difficult to conduct because they demand considerable and prolonged lifestyle changes from the participants. Initial studies must therefore focus on cellular endpoints related to colon carcinogenesis in small groups of persons. Epithelial cell proliferation measured by labeling of S-phase cells in colon crypts with $[^3H]$thymidine is a biomarker that has been related to colon neoplasia and serves as an intermediate endpoint in human studies (17). This biomarker responds to caloric manipulations in rodents and is reduced by caloric restriction (18, 19) or starvation (20, 21). We have shown that modest caloric restriction in rats lowers colonic epithelial proliferation in parallel with a reduction in induced tumor incidence (22). This occurred with both high- and low-fat diets. Changes in colonic cell proliferation in response to caloric restriction may also correspond to altered risk of colon cancer in humans.

Since caloric intake contributes to experimental colonic carcinogenesis, it has been postulated that other determinants of metabolic balance such as RMR and exercise as well as endpoints of metabolic balance, such as body composition, body weight, and BMI, may relate to risk. Epidemiological and animal studies have addressed some of these issues (15, 23–26), but biological data on the relationship of these parameters to cancer risk in humans are needed.

In the study reported here, we examined the effect of caloric restriction on rectal epithelial cell proliferation and the relationship of cell proliferation indices to RMR, BMI, and body composition in obese persons.

MATERIALS AND METHODS

Patient Selection. Patient inclusion criteria were body weight of more than 130% of ideal body weight and willingness to sign informed consent. Criteria for exclusion were any of the following: a family history of familial adenomatous polyposis or hereditary nonpolyposis colon cancer, a personal history of colon polyps or cancer, inflammatory bowel disease, diabetes mellitus, calcium supplementation of more than 200 mg elemental calcium/day or daily use of aspirin or nonsteroidal anti-inflammatory drugs. The study was approved by the St. Luke’s-Roosevelt Hospital Center institutional review board.

Study Design. Colonic epithelial proliferation in rectal biopsies was measured at baseline in obese persons who presented to the Obesity Research Center at St. Luke’s-Roosevelt Hospital Center in New York for obesity counseling or evaluation for various weight reduction protocols. Follow-up biopsies were performed in patients who specifically enrolled in the behavior modification weight reduction program and who successfully reduced their caloric intake by a mean of 15% or more continuously for 12 weeks as evidenced by food diaries and weight reduction. Baseline evaluation also included medical history and physical examination, psychological testing, blood chemistry, complete blood count, thyroid function tests, and measurement of RMR and body composition.

Diet Modification. The weight reduction program consisted of 16 consecutive weekly group and/or individual sessions supervised by a dietitian specializing in weight control. The initial 4 weeks of the program consisted of dietary and behavioral assessment, and this was followed by 12 weeks of caloric restriction. The subjects were initially prescribed a caloric management goal equivalent to their RMR. Reduction in caloric intake of normally consumed foods was achieved by behavior modification combined with nutrition counseling provided at the weekly meetings. Food and activity records were prepared by the subject for 3 days per week. No appetite suppressing medications were permitted. The emphasis was on reducing total caloric intake to the prescribed caloric goal.

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3 The abbreviations used are: RMR, resting metabolic rate; BMI, body mass index.

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Special Studies. Proctoscopy and rectal biopsies were performed between 8 and 10 a.m. after an overnight fast and a tap-water enema. Biopsies were oriented with a dissecting microscope; cut into 1.5-mm-thick sections; incubation of crypts were scored for crypt depth (total number of cells per colon crypt column) and for the number and position of labeled S-phase nuclei, by a research assistant blind to the study. Biopsies were processed for autoradiography until >20 cryps/patient sample were attained or until the tissue was exhausted. The labeling index (the percentage of labeled cells per crypt column) was calculated for the whole crypt column and for each of 5 longitudinal crypt compartments (compartment 1 at the base of the crypt and compartment 5 near the lumenal surface).

Ideal body weight was determined from the 1959 Metropolitan Life Insurance tables. BMI was calculated as body weight in kg divided by the square of the height in meters (kg/m²). RMR was measured in a quiet thermoneutral room by indirect calorimetry using a Horizon Metabolic Measurement Cart (SensorMedics Corp., Sunnyvale, CA). Body fat was calculated based on total body electrical conductivity. Diet composition and percentage reduction in caloric intake were calculated by a trained nutritionist from food records using Nutritionist III software. Estimation of percentage of caloric restriction based on the subjects’ RMR and weight change yielded similar results.

Statistics. Differences between groups were analyzed by unpaired t tests. The relationship of age, BMI, RMR, and body composition to labeling index was calculated using univariate and multivariate regression analyses.

RESULTS

Characteristics of Study Populations. Baseline rectal epithelial proliferation measurements for comparison with BMI, RMR, and body composition were available for 35 subjects with a mean age of 45.6 years. Their mean BMI was 35.6 kg/m² (normal, 18–28 kg/m²), and their mean RMR was 1646 kcal/day. Their body mass was 40.7% fat. Similar characteristics were noted at baseline in the subgroup of 8 evaluable patients who completed 12 weeks of caloric restriction (Table 1).

Nutritional Data. At baseline, the mean caloric intake of the caloric-restricted subjects was 2406 kcal/day. After caloric restriction, this was reduced by 34% to 1591 kcal/day, similar to their calculated resting metabolic rate (Tables 1 and 2). Mean body weight decreased by 8.6% (ranging from 4 to 12%). The distribution of fat, carbohydrate, and protein in the diet at baseline varied among the subjects, but diet modification resulted in no significant change in the percentage of calories derived from these macronutrients (Table 2).

Rectal Proliferation Data. At baseline, epithelial proliferation measured as the labeling index and the number of 3H-labeled cells per crypt column was within the normal range reported in the literature and in our laboratory. The mean labeling index was 6.5% in the total group of 35 obese subjects and 6.8% in the 8 evaluable subjects who underwent caloric restriction. After caloric restriction, the labeling index of the whole colonic crypt decreased by 39% (P < 0.001), and the labeling index of the upper 40% of the crypt decreased by 57% (P < 0.05) (Table 3; Fig. 1). The rectal crypt depth did not change. The labeling index in the total group of 35 subjects at baseline was unrelated to age (r = −0.08), BMI (r = 0.14), RMR (r = 0.17), or percentage of body fat (r = 0.12), by multivariate regression analysis.

DISCUSSION

Dietary intake of calories and of fat are correlated with risk of colon cancer in animal experiments and in population and case-control studies in humans. Early epidemiological data suggested that populations with high fat and caloric intake were at increased risk of colon neoplasia (12, 28). This observation was supported by case-control studies (13–16), with some exceptions (29). Recently, a prospective dietary study of American nurses found an increased risk of colon cancer in those consuming animal fat more frequently (30). In epidemiological studies, it is difficult to separate the effects of fat from those of caloric intake. When these factors are studied experimentally in rodents, it appears that caloric and fat intake are independent contributors to risk. Corn oil and lard promote the development of...
carcinogen-induced colon tumors in rats fed isocaloric diets (10, 31).
Lowering caloric intake by 40% of an ad libitum diet independent of total fat intake also reduces the incidence of colon tumors in carcinogen-treated rats (8). These studies raise the key question of whether human dietary guidelines should include a reduction in calories in addition to a reduction in fat intake.

In the present study, caloric restriction reduced rectal epithelial proliferation indices in obese persons. The rate of cell replication has been associated with carcinogenic propensity (32). In the colon, the rate and pattern of epithelial proliferation, measured by labeling S-phase cells in colonic crypts, have served as intermediate endpoints in both animal and human studies (17). Lipkin (33) and Deschner et al. (34) described phases of abnormal colonic proliferation that precede the development of neoplasia. Initially they observed an upward expansion of the proliferative zone evidenced by an increased number of S-phase cells near the luminal surface of the crypt. This was followed or accompanied by an increase in the total crypt population of proliferating cells. Such changes in colonic epithelial proliferation have been associated with tumor promotion in animal models (35) and with conditions of increased risk in humans, including persons with familial colon cancer (34) and those with sporadic colon cancer (36) or adenomatous polyps (37). Interventions that reduce total-crypt or upper-crypt labeling indices are considered favorable (38), although large prospective studies to validate this hypothesis are still pending.

Since long term caloric restriction studies in humans are difficult to conduct, the present study focused on changes in intermediate biomarkers related to colon carcinogenesis in a small group of obese persons who had an inherent interest in reducing their food intake. Only patients who succeeded in reducing caloric intake and losing weight were selected. Whether similar results would be obtained in persons with normal BMI values and whether colon tumor incidence in humans would decrease with reduced caloric intake remain to be studied.

The correlation of energy intake with colon cancer risk raises the question of whether parameters of energy expenditure and storage also influence carcinogenesis. These factors include RMR, exercise, thermogenesis, BMI, body composition, and as yet poorly defined aspects pertaining to efficiency of energy utilization. Some studies have addressed these issues. Physical activity has been inversely correlated with colon cancer risk in some studies in humans (39, 40) and in animals (23, 24). The relationship of resting metabolic rate or thermogenesis to colon cancer risk is unknown. Epidemiological studies have shown a weak association between the upper range of BMI and increased colon cancer risk, although the data have not been consistent (15, 16, 25, 26, 41). It remains puzzling that the apparent association of risk with fat and energy intake does not translate to a strong correlation of excess weight with cancer risk. Studies which focus on the parameters of energy expenditure and storage in relation to cancer risk are needed.

No correlation of RMR, BMI, or body composition with rectal epithelial proliferation indices was found in the present study. This may reflect the limitations of colonic proliferation measurements and biologic indicators of energy balance in predicting risk as well as the complex nature of their possible interactions. Though tumor development may be influenced by genetic and environmental factors, including diet composition and energy balance, the complex summation of these interactions is unlikely to be reflected by a single physiological measurement that precedes neoplastic transformation. Nonetheless, interventions that reduce parameters associated with risk should be considered positive and serve as a basis for cancer prevention strategies.

Epidemiological studies that correlate colon cancer risk with dietary caloric and fat intake suggest that lowering intake may reduce risk. This study provides initial biological data in obese persons to support this hypothesis. Long term prospective studies using colon polyps or cancer as endpoints are needed to more clearly define the role of caloric restriction in colon cancer prevention.

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