[CANCER RESEARCH 52, 3589–3592, July 1, 1992]

Meal Frequency and Risk of Colorectal Cancer[1]

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ABSTRACT

The relation between meal frequency and the risk of colorectal cancer was investigated in a case-control study conducted in North Italy on 889 cases of colon cancer, 581 cases of rectal cancer, and 2475 controls admitted to hospital for acute, nonneoplastic, or digestive disorders. As compared to individuals who reported 2 or fewer meals per day, the multivariate colon cancer odds ratios were 1.7 [95% confidence interval (95% CI), 1.5–2.1] for 3, and 1.9 (95% CI, 1.1–3.3) for 4 meals or more. Corresponding rectal cancer odds ratios were 1.4 (95% CI, 1.1–1.7) for 3, and 1.9 (95% CI, 1.1–3.5) for 4 meals or more. The direct trends in risk of colorectal cancer with frequency of eating were not substantially modified by allowance for various dietary and nondietary potential confounding factors, including an approximate measure of total energy intake, and did not show significant effect modification across strata of age, sex, education, and other major risk covariates. A role of meal frequency in the etiology of colorectal cancer is biologically plausible, since when a meal is eaten, the gallbladder contracts and releases bile acids. Thus, eating patterns can influence the enterohepatic circulation and, consequently, the exposure time of intestinal mucosa to bile acids.

INTRODUCTION

Differences in diet have been suggested to account for the majority of the variation in rates of colorectal cancer among countries (1, 2). A large number of case-control studies and prospective investigations have suggested that diets high in fat and/or meat (3) and low in vegetables and/or whole-grain cereals (4) enhance the probability of developing colorectal cancer.

The specific factor(s) involved in such consistent dietary associations are still unknown and it is plausible, according to the widely held hypothesis which attributes to bile acids a crucial role in colorectal cancer causation, that not only the quantity and quality of food intake but also the eating pattern is important. Indeed, the rhythm of the enterohepatic circulation is largely determined by the number of daily meals (5). Only three epidemiological studies have so far shown a detailed analysis of colorectal cancer risk according to frequency of meals (6–8). Increases of approximately 50% in risk of cancer of the colon in individuals reporting a higher meal frequency have already been reported, that persisted after allowance for various covariates [*e.g.*, total energy intake (6), combined food scores (8), etc.].

In order to contribute to this issue, we have examined the relation of risk of cancer of the colon and rectum with daily frequency of meals in a case-control study conducted in the Northern part of Italy.

PATIENTS AND METHODS

The present data were derived from an ongoing case-control study of several neoplasms of the digestive tract based on a network of teaching and general hospitals from Greater Milan area and Pordenone province, North Italy (8–12). Recruitment of cases of colorectal cancer started in January 1985. All the interviews were conducted in hospital before December 1990 and approximately 2% of cases and 3% of control subjects refused to be interviewed.

The cases studied were subjects with histologically confirmed large bowel cancer diagnosed within the 6 months preceding interview (median time between cancer diagnosis and interview, 25 days). Altogether, 889 patients with colon cancer and 581 with rectal cancer were interviewed. The median age was 61 years for colon cancer and 62 for rectal cancer.

The comparison group comprised 2475 patients with a median age of 56 years. No individual matching was performed, but the catchment areas of cases and controls were strictly comparable, *i.e.*, control subjects would have been referred, if affected by large bowel cancer, to the hospitals where cases were contacted. None of the control subjects had malignant tumors, digestive tract disorders, or any condition related to alcohol and tobacco consumption, or which might have resulted in long-term modification of diet. The main diagnostic categories were: trauma (40%); nontraumatic orthopedic disorders (19%); acute surgical conditions, including plastic surgery (17%); eye disorders (13%), and other illnesses such as diseases of the ear, nose, skin, or teeth (12%).

A standard questionnaire was used to obtain information on sociodemographic factors, general characteristics, life-style habits, including smoking, alcohol, and coffee, and related personal and family medical history. Further, patients were asked about their consumption per week of 40 foods and beverages (including major sources of starch, proteins, fat, vitamins, and fiber in the Italian diet) and frequency of daily meals before the onset of the disease which led to the current admission. Intake of any solid food, but not of low-caloric beverages such as coffee or tea only, was considered a meal, irrespective of serving size.

Data Analysis and Control of Confounding Variables. ORs[3] of cancer of the colon and rectum, together with their 95% approximate CIs, according to daily meal frequency were computed by means of unconditional multiple logistic regression equations with maximum likelihood fitting (13, 14). Allowance was made, (*a*) for age, sex, and area of residence; (*b*) also for potential confounding variables (*i.e.*, education, body mass index (kg/m^2), approximate tertiles of total energy, and red meat intake). Total energy intake was estimated approximately by multiplying the frequency of consumption per week of the 40 available foods and beverages (alcoholic beverages included) by their average energy content in kcal. The total intake of red meat, an indicator of level of intake of proteins and fat of animal origin, included the consumption of beef and pork from all available sources (*i.e.*, beef, liver, raw ham, boiled ham, salami, and sausage).

RESULTS

The distribution of cases of colorectal cancer and controls by age, sex, education, area of residence, and approximate intake of total energy and red meat is shown in Table 1. Cases of rectal cancer, but not colon cancer patients, reported fewer years of education as compared to control subjects. Both cases of colon and rectal cancer consumed red meat significantly more frequently than the control group (Table 1).

Received 1/10/92; accepted 4/22/92.

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[1] The work was supported by the framework of the Italian National Research Council (CNR) Applied Project Clinical Application of Oncological Research, and with the contribution of the Italian Association for Cancer Research and the Italian League against Tumours, Milan.

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[3] The abbreviations used are: OR, odds ratio; CI, confidence interval.

Table 1 *Distribution of 889 cases of colon cancer, 581 of rectal cancer, and 2475 controls according to various characteristics, North Italy 1985–1990*

Variable	Cancer				Controls	
	Colon		Rectum			
	No.	%	No.	%	No.	%
Age (yr)						
<40	43	4.8	20	3.4	273	11.0
40–49	109	12.3	55	9.5	486	19.6
50–59	237	26.7	152	26.2	745	30.1
60–69	328	36.9	234	40.3	732	29.6
70–74	172	19.3	120	20.7	239	9.7
Sex						
Males	460	51.7	349	60.1	1591	64.3
Females	429	48.3	232	39.9	884	35.7
Education (yr)[a]						
<5	122	13.7	106	18.3	341	13.8
5–8	545	61.4	370	63.8	1555	62.9
≥9	221	24.9[b]	104	17.9	578	23.4
Area of residence						
Milan	766	86.2	456	78.5	1776	71.8
Pordenone	123	13.8	125	21.5	699	28.2
Total energy intake (kcal/day)						
<1800	285	32.1	193	33.2	765	30.9
1800–2399	358	40.3	207	35.6	863	34.9
≥2400	246	27.7	181	31.2	847	34.2
Red meat intake (weekly frequency)						
≤6	282	31.7	212	36.5	958	38.7
7–8	272	30.6	168	28.9	758	30.6
≥9	335	37.7[b]	201	34.6[b]	759	30.7

[a] The sum of strata does not add up to the total because of missing values.
[b] As compared to control subjects, $\chi^2_2 > 9.21$; $p < 0.01$.

Table 2 *Odds ratio of cancer of the colon and rectum by daily meal frequency, North Italy, 1985–1990*

Daily meal frequency	Cancer		Controls, no.	Odds ratio (95% confidence interval)			
				Colon		Rectum	
	Colon, no.	Rectum, no.		Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]
≤2[c]	543	364	1707	1[d]	1[d]	1[d]	1[d]
3	325	199	701	1.8 (1.5–2.2)[e]	1.7 (1.5–2.1)	1.5 (1.2–1.8)	1.4 (1.1–1.7)
≥4	20	18	61	2.2 (1.3–3.9)	1.9 (1.1–3.3)	2.2 (1.2–3.9)	1.9 (1.1–3.5)
χ^2_1 (trend)				45.9[f]	38.5[f]	16.0[f]	13.7[f]

[a] Multiple logistic regression estimates adjusted for age, sex, and area of residence.
[b] Multiple logistic regression estimates adjusted for age, sex, education, area of residence, body mass index, approximate total energy, and red meat intake.
[c] The sum of strata does not add up to the total because of missing values.
[d] Reference category.
[e] 95% confidence interval.
[f] $P < 0.001$.

The role of eating pattern on both cancers of the colon and rectum is considered in Table 2. For colon cancer the multivariate OR was 1.7 (95% CI, 1.5–2.1) for three and 1.9 (95% CI, 1.1–3.3) for four meals or more per day compared with two or fewer. Corresponding values for rectal cancer were 1.4 (95% CI, 1.1–1.7) for three and 1.9 (95% CI, 1.1–3.5) for four meals or more per day (Table 2). Adjustment for intake of several other food items (*i.e.*, cheese, various fruits and vegetables, starchy foods, and alcoholic beverages) was also performed but is not shown since it left the results substantially unchanged.

Table 3 shows the effect of meal frequency across different strata of age, sex, education, body mass index, area of residence, and the most important dietary determinants of risk of colorectal cancer in the present study (*i.e.*, total energy intake and red meat intake). No significant effect modification between meal frequency and the examined covariates emerged, although there was a hint that the effect of frequent eating may be stronger in women than men and in individuals with lowest weight than heavier people. Still, all ORs for both colon and rectal cancer were above unity for subjects who reported three or more meals per day.

DISCUSSION

The present study indicates that eating pattern, aside from any qualitative and quantitative aspects of habitual diet, may be relevant to the etiology of colorectal cancer. The strength of the association, with an approximately 2-fold elevated risk for meal frequency ≥4 *versus* ≤2, is similar to that observed with the best recognized dietary determinants of colorectal cancer, such as fat or red meat (as risk factors) or vegetables (as protective factors). In previous studies (6, 7) on the same issue,

Table 3 *Odds ratio[a] of cancer of the colon and rectum by daily meal frequency in separate strata of age, sex, and selected covariates, North Italy, 1985–1990*

Covariate	Colon cancer		Rectal cancer	
	Odds ratio (≥3 *vs.* ≤2 daily meals)	95% confidence interval	Odds ratio (≥3 *vs.* ≤2 daily meals)	95% confidence interval
Age (yr)				
<50	2.9	2.0–4.3	2.5	1.5–4.3
50–59	1.7	1.2–2.3	1.6	1.1–2.3
60–69	1.6	1.2–2.1	1.3	0.9–1.8
≥70	1.7	1.1–2.6	1.3	0.8–2.1
Sex				
Males	1.5	1.2–1.9	1.2	0.9–1.6
Females	2.4	1.8–3.2	2.1	1.5–2.9
Education (yr)				
<6	1.9	1.5–2.5	1.5	1.2–2.0
≥6	1.8	1.4–2.3	1.4	1.0–1.9
Body mass index (kg^{-2})				
<26	2.5	1.9–3.3	2.4	1.7–3.4
≥26	1.6	1.3–2.0	1.1	0.9–1.4
Area of residence				
Milan	2.0	1.6–2.4	1.6	1.2–2.0
Pordenone	1.4	0.9–2.0	1.2	0.8–1.8
Total energy intake (kcal/day)				
<1800	1.8	1.3–2.6	1.4	1.0–2.2
1800–2399	2.1	1.6–2.8	1.7	1.2–2.4
≥2400	1.3	1.0–1.8	1.3	0.9–1.8
Red meat intake (weekly frequency)				
≤6	1.7	1.3–2.4	1.6	1.1–2.2
7–8	2.0	1.4–2.6	1.8	1.0–2.2
≥9	1.7	1.3–2.3	1.3	0.9–1.9

[a] Estimates from multiple logistic regression adjusted for age, sex, and area of residence, as appropriate.

categories of meal frequency different from ours were chosen, presumably reflecting differences in eating patterns among Australia, the United States, and Italy. Still, a similar magnitude of the risk emerged from those investigations and from a preliminary analysis of the present data set (8). Also consistently, such risk elevation persisted after allowance for various dietary and nondietary potential confounding factors and was apparently more marked for colon than for rectal cancer.

Despite receiving relatively little attention in previous epidemiological work, an effect of meal frequency on colon cancer risk is also suggested by much *in vitro* as well as animal and human data (15, 16), that point to the role of bile acids in colorectal carcinogenesis. Bile acids act as promoters of colon tumors in mutagenesis assay systems and in various animal models. Furthermore, in humans the protective effects of diets low in fat and refined carbohydrates but high in fiber and/or vegetables and, possibly, calcium, can be also interpreted in terms of their influence on stool bulk, bile acid output, and, consequently, on bile acid concentration (2–4, 17).

When a meal is eaten, the gallbladder contracts and releases primary bile acids into the small intestine. Bile acids are mainly reabsorbed into the blood by an active process in the terminal ileum. However, small amounts of bile acids pass into the colon, where they serve as substrate for intestinal bacteria and are converted into secondary bile acids.

Further, increased bile acid production follows elevated fat consumption, the extent depending on various host factors that influence the conversion of cholesterol into bile acids (16). Thus, serum cholesterol is inversely correlated with fecal bile concentration (16, 18), suggesting that people with low serum cholesterol have efficient hepatic clearance, resulting in a higher concentration of bile acids in the feces and, possibly, an enhanced colon cancer risk (18). More frequent meals result in more frequent release of bile and are associated with reduced serum cholesterol levels (18). Also, the potential protection of coffee against colon cancer has been interpreted in terms of reduction of bile acid and neutral sterol secretion induced by substances in the coffee (9, 19).

Certain limitations of the present study can be acknowledged, but are unlikely to account for the findings. The choice of hospital controls, for instance, has long been debated (20), particularly in relation to the analysis of life-style habits or diet. However, care was taken in obtaining unselected groups of cancer cases and of controls from the same catchment areas. In addition, digestive disorders and diseases that might alter dietary habits were excluded from the control group. The possibility was also excluded of there being inconsistencies in the findings among the controls between major diagnostic subgroups. Participation was practically complete and information bias should not have distorted the present results, since the relation of meal frequency with colorectal cancer risk is not widely known.

Of greater concern is the limited food list which provides information only on frequency of consumption of certain foods and beverages that were of interest *a priori* (12, 21). Consequently, only an approximate estimate is possible for total energy intake and intake of other relevant foods (*e.g.*, red meat) (22). However, the direct association between colorectal cancer risk and meal frequency was modified little, if at all, by allowance for potential confounding factors, including dietary habits and alcoholic beverage consumption. If frequent eating is confirmed as a risk factor, at least in coexistence with a fat-rich Western diet (23–25), it would provide a relevant indication from a preventive viewpoint, and would illustrate a principle of major importance in the understanding of the etiology of cancer of the large bowel.

ACKNOWLEDGMENTS

The authors wish to thank Dr. Leo Kinlen for his comments and Ilaria Calderan and Anna Redivo for editorial assistance.

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