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Macronutrients and colorectal cancer: a Swiss case-control study

F. Levi[1]*, C. Pasche[1], F. Lucchini[1] & C. La Vecchia[2]

[1]*Registre Vaudois des Tumeurs, and Unité d'épidémiologie du cancer, Institut universitaire de médecine sociale et préventive, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland;* [2]*Istituto di Ricerche Farmacologiche 'Mario Negri', Milano; and Istituto di Statistica Medica e Biometria, Università degli Studi di Milano, Milano, Italy*

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Background: A role of energy and various nutrients, including protein, sugar, saturated and unsaturated fats, in colorectal cancer risk has been suggested, but should be better defined.

Patients and methods: The association between dietary intake of various macronutrients and colorectal cancer risk was analysed using data from a case-control study conducted between 1992 and 2000 in the Swiss Canton of Vaud. The study comprised 286 case subjects (174 males, 112 females; median age 65 years) with incident, histologically confirmed colon (n = 149) or rectal (n = 137) cancer, and 550 control subjects (269 males, 281 females; median age 59 years) admitted to the same University Hospital for a wide spectrum of acute non-neoplastic conditions. Dietary habits were investigated using a validated food frequency questionnaire, including questions on 79 foods or recipes and on individual fat intake pattern. Multivariate odds ratios (OR) were obtained after allowance for age, sex, education, physical activity and energy intake.

Results: The risk of colon and rectal cancer increased with total energy intake (OR in highest and lowest tertile, 2.0 and 2.2, respectively). There was no significant relation with starches or proteins, a significant inverse relation with sugars (OR for the highest tertile, 0.5), a direct trend in risk of borderline significance for saturated fats (OR = 1.4 for the highest tertile), and significant inverse trends for monounsaturated (OR = 0.6) and polyunsaturated fats (OR = 0.6).

Conclusions: These findings confirm that energy intake is directly related to colorectal cancer risk, and that different types of fat may have different roles in colorectal carcinogenesis.

Key words: case-control study, colorectal carcinoma, diet, Switzerland

Introduction

Most epidemiological research on diet and colorectal cancer has been focused on specific foods or micronutrients. Thus, a risk score based on the Health Professionals' Follow-up Study included body mass index, physical activity, folic acid, alcohol, smoking and red meat consumption [1].

A factor analysis based on a large case-control study from Northern California, Utah and Minnesota [2] included several foods (meats, eggs, margarine, etc.) to define diets at different risk for colorectal cancer.

However, the role of energy and macronutrients has also been considered in colorectal carcinogenesis. A report from the Nurses' Health Study published in 1990 [3] showed that, after adjustment for total energy intake, consumption of animal fat was associated with increased risk of colorectal cancer, but no association was found with vegetable fat. A comprehensive report from the World Cancer Research Fund and the American Institute for Cancer Research [4] concluded that total energy has no simple relation with colorectal cancer risk, that the data were inconsistent for carbohydrates, cholesterol and proteins, and that diets high in total fat (and specifically saturated fat) possibly increase risk.

In a subsequent Italian case-control study, the risk of cancer of the colon and rectum increased with total energy intake, as well as with starch intake. Monounsaturated fats appeared uninfluential, while saturated fats showed a modest direct association, and polyunsaturated fats an inverse one [5, 6].

In a multicenter American case-control study [7], some association with selected types of fats was reported only for women who had a family history of colorectal cancer. No consistent association with fat was observed in the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, including 185 cases of colorectal cancer [8]. Saturated fatty

**Correspondence to:* Dr F. Levi, Registre Vaudois des Tumeurs, and Unité d'épidémiologie du cancer, Institut universitaire de médecine sociale et préventive, Centre Hospitalier Universitaire Vaudois, Falaises 1, CH-1011 Lausanne, Switzerland, Fax: +41-21-323-03-03; E-mail: Fabio.Levi@inst.hospvd.ch

Table 1. Distribution of 149 colonic and 137 rectal cancer cases, and of 550 controls according to sex and age group; Vaud, Switzerland, 1992–2000

Age (years)	Cases				Controls	
	Colon		Rectum			
	Males	Females	Males	Females	Males	Females
<45	4	3	5	5	32	49
45–54	8	9	13	10	66	58
55–64	23	17	29	11	90	76
65–74	54	31	38	26	81	98

acids were also related to colorectal cancer risk in a study from Argentina [9], and sucrose in another from Uruguay [10].

To provide further information on the issue, we analysed data from a case-control study conducted in Switzerland.

Materials and methods

The data were derived from a case-control study of colorectal cancer conducted between January 1992 and December 2000 in the Swiss Canton of Vaud [11, 12].

Cases comprised 286 patients (174 males, 112 females) with incident, histologically confirmed colon (ICD-0 9th Revision: 153.0–153.9; $n = 149$) or rectal (ICD-0 9th Revision: 154.0–154.1; $n = 137$) cancer (age range 26–74 years; median age 65 years) who had been admitted to the University Hospital of Lausanne, Switzerland.

Controls were subjects residing in the same geographical area, whose admission diagnosis was of acute, non-neoplastic diseases, and unrelated to long-term modification of diet. A total of 550 subjects (269 males, 281 females) aged <75 years (range 27–74 years; median age 59 years) were interviewed. They were admitted to the University Hospital of Lausanne for a wide spectrum of acute conditions, including traumas (33%, mostly sprains and fractures), non-traumatic orthopaedic conditions (31%, mostly low back pain and disk disorders), surgical conditions (19%, mostly abdominal, such as acute appendicitis, kidney stones or strangulated hernia), and miscellaneous other disorders (17%, including acute medical, eye, nose and throat, and skin diseases).

All interviews were conducted in hospital during the admission diagnosis. Sixteen per cent of subjects (16% of cases, 15% of controls) approached for interview refused. The structured questionnaire included information on socio-demographic characteristics and lifestyle habits (e.g. smoking, alcohol consumption and physical exercise [13]), and anthropometric factors. A problem-oriented medical history was also included. An interviewer-administered food-frequency questionnaire (FFQ) [14–16] was used to assess subjects' habitual diet. Information was elicited on average weekly frequency of consumption of specific foods, as well as complex recipes (including the most common ones in the Swiss diet) during the 2 years prior to cancer diagnosis or hospital admission (for controls). The FFQ included 79 foods, food groups or recipes. Specific questions aimed at assessing fat-intake pattern were also included.

To compute energy and nutrient intake, standardized portion sizes and food-composition databases [17] were used for ~80% of food items. These sources had to be integrated with data on traditional food products, as well as information from manufacturers.

Statistical analysis

Odds ratios (OR) and the corresponding 95% confidence intervals (CI) were computed, using unconditional multiple logistic regression models [18]. Various types of macronutrients were entered in the models both as tertiles of the distribution of controls and continuously [19]. Several models were fitted to the data, all of which included terms for age, sex, education, physical activity, and total energy according to the residual model [20]. Inclusion in the models of other variables, such as body mass index, family history of colorectal cancer and, for women, parity and age at first birth, did not materially modify any of the estimates.

Results

Table 1 gives the distribution of colon and rectal cancer cases, and of controls by sex and age group.

Table 2 gives the distribution of cases of colon and rectal cancer, and also the control group, according to tertile of total energy intake. It also gives the corresponding ORs. In the highest tertile, these were 2.0 (95% CI 1.2 to 3.2) for colon, 2.2 (95% CI 1.3 to 3.6) for rectum, and 2.0 (95% CI 1.3 to 2.9) for all colorectal cancers, and the trends in risk were significant.

Table 3 gives the energy-adjusted distribution of cases and controls in subsequent intake tertiles of various nutrients, the upper cut points of tertiles, and the corresponding multivariate ORs. There was no significant relation with starches or proteins, and an inverse relation with sugars (OR = 0.5 for the highest tertile). With reference to fats, a direct trend in risk of borderline significance was observed for saturated fats (OR = 1.4, 95% CI 0.9 to 2.2, for the highest tertile), whereas significant inverse trends were observed for monounsaturated (OR = 0.6, 95% CI 0.4 to 0.9) and polyunsaturated fats (OR = 0.6, 95% CI 0.4 to 0.9). The confidence intervals of the upper tertiles, as well as of the beta estimates of the corresponding trends, do not overlap. For polyunsaturated fats, the inverse relation was apparently stronger for colon (OR = 0.5, 95% CI 0.3 to 0.8) than for rectal (OR = 0.7, 95% CI 0.4 to 1.3) cancer, while no appreciable difference was observed for other nutrients.

Table 2. Distribution[a] of 149 colon and 137 rectal cancer cases, and of 550 controls according to tertile of total energy (KCal/day) intake, and the corresponding odds ratios (OR)[b] and 95% confidence intervals (95% CI)

Total energy intake tertile (upper cut point; KCal/day)[c]	Colon cancers	Rectal cancers	Controls	OR (95% CI)[b]		
				Colon	Rectum	Colon and rectum
I tertile (lowest; 1714 KCal)	38	31	181	1[d]	1[d]	1[d]
II tertile (2329 KCal)	42	45	183	1.1 (0.7–1.8)	1.5 (0.9–2.5)	1.3 (0.8–1.9)
III tertile (highest)	69	61	186	2.0 (1.2–3.2)	2.2 (1.3–3.6)	2.0 (1.3–2.9)
$X^2_{1\ (trend)}$				6.6[e]	8.4[f]	10.7[f]
Continuous OR (×100 KCal)				1.05 (1.02–1.07)	1.04 (1.01–1.07)	1.04 (1.02–1.06)

[a]Data from Vaud, Switzerland, 1992–2000.
[b]Estimates from multiple logistic regression models including terms for sex, age, education and physical activity.
[c]Upper tertile cut point based on distribution among controls.
[d]Reference category.
[e]P <0.05.
[f]P <0.01.

Table 3. Multivariate energy-adjusted frequency distribution and upper cut points of intake, odds ratios (OR)[a] and corresponding 95% confidence intervals (95% CI) for subsequent intake tertiles of various macronutrients, among 286 colorectal cancer cases and 550 controls[b]

Nutrient	Upper cut points of intake (g/day)[c] No. of cases: No. of controls in tertile			ORs[a] (95% CI) in tertile			$X^2_{1\ (trend)}$
	I (lowest)	II	III (highest)	I (lowest)	II	III (highest)	
Protein	282	372		1[d]	0.8	1.1	0.4
	96:181	69:181	121:188		(0.5–1.3)	(0.7–1.7)	
Sugar	267	396		1[d]	0.4	0.5	9.6[f]
	136:181	63:182	87:187		(0.3–0.7)	(0.3–0.9)	
Starch	422	621		1[d]	0.9	0.8	0.5
	104:182	92:181	90:187		(0.6–1.3)	(0.5–1.4)	
Monounsaturated fat	249	335		1[d]	0.9	0.6	6.0[e]
	105:182	99:181	82:187		(0.6–1.4)	(0.4–0.9)	
Saturated fat	205	312		1[d]	1.0	1.4	2.6
	90:182	84:181	112:187		(0.7–1.6)	(0.9–2.2)	
Polyunsaturated fat	138	194		1[d]	1.0	0.6	5.1[e]
	93:182	106:181	87:187		(0.7–1.5)	(0.4–0.9)	

[a]Estimates from multiple logistic regression equations including terms for age, sex, education, physical activity and residual energy.
[b]Data from Vaud, Switzerland, 1992–2000.
[c]Based on the distribution among controls.
[d]Reference category.
[e]P <0.05.
[f]P <0.01.

Discussion

In this study, total energy intake was directly related to colorectal cancer risk, confirming the results of previous case-control studies [5, 7] and the observation that calorie restriction reduces cancer incidence in rodents [21, 22] and colorectal cell proliferation in humans [5, 23–25]. Energy intake, in fact, can be responsible for glycaemic overload and a compensatory increase of serum insulin and related insulin growth factor-1 (IGF-1), which is a promoter of tumour cell growth *in vitro* [23, 25], and may expose colonic and rectal cells to a proliferative stimulus [26, 27]. Diabetes has also been related to increased colorectal cancer risk [26, 28].

The pattern of risk, moreover, was different for various types of fats. A non-significant direct association was observed with saturated fats, confirming the results of the Nurses' Health Study [3], of a large case-control study from Italy [5], and another case-control study from Argentina [9]. Other studies

[7, 8, 23] did not, however, find any consistent relationship with saturated fats. Whether this is partly or largely due to the different models used for energy allowance [5, 19] or to other baseline differences in the study design and population investigated—apart from the factor of chance—remains open to discussion. In contrast, poly- or monounsaturated fatty acids showed a more favourable pattern of risk, confirming previous observations [3–5] and further indicating that the type and composition of dietary fat may appreciably influence an individual's risk of colorectal cancer. Such diverging results can hardly be accounted for by greater energy intake in cases.

The results of epidemiological studies are, however, apparently at variance with the results of experimental studies in rodents, which have shown an increase in the incidence of chemically induced colon cancer in animals upon high polyunsaturated fat intake [30]. It is known, however, that the consumption of polyunsaturated fatty acids has a role, too, since n-3 fatty acids seem to have a more favourable effect compared with n-6 fatty acids [31–33].

The favourable effect of unsaturated fatty acids was apparently stronger in the colon, confirming previous observations [5, 29], and was potentially related to the influence of fat type on entero-hepatically circulating bile acids.

The inverse relationship with sugars can be related to the protection of fruits on colorectal cancer risk in these individuals [11], since fruits are the major source of sugar [17, 34].

Dietary habits of hospital controls may differ from those of the general population, but we excluded from the comparison group all diagnoses that may have involved long-term dietary modification. Among other strengths of this study, there are the satisfactory reproducibility and validity of the FFQ [15, 16], the comparable catchment area of cases and controls, the high participation rate, and the possibility of allowance for several relevant covariates in the analyses.

In conclusion, therefore, the findings of the present study confirm that energy intake is directly related to colorectal cancer risk, providing epidemiological support to *in vitro* observations and animal experiments [21–23, 26, 27]. They also confirm [6] that different types of fat may have different roles in colorectal carcinogenesis. The favourable role of (mono)unsaturated fatty acids may also explain some of the geographic variation in colorectal cancer rates, including the comparatively low rates in Mediterranean countries [35–37].

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