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Diet and Colorectal Cancer: Results of Two Case-control Studies in Russia

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Two case-control studies of diet and colorectal cancer were conducted in Moscow and Khabarovsk. The Moscow study comprised 100 cases of colorectal cancer and 100 neighbourhood controls. The Khabarovsk study consisted of 117 cases of colorectal cancer and 117 population controls. A history of the usual dietary intake one year prior to interview was taken using a food frequency questionnaire. Effects were adjusted in analysis for energy intake and education. Significantly reduced risks were observed with high intakes of cellulose ($P = 0.001$), beta-carotene ($P = 0.002$), vitamin C ($P = 0.007$), polyunsaturated fatty acids (PUFA) ($P = 0.004$), cholesterol ($P = 0.04$), and with a high ratio of PUFA to saturated fatty acids (SFA) ($P = 0.002$). Significant increases in risk were observed in association with high ratios of intakes of protein to cellulose ($P = 0.002$) and of fat to cellulose ($P = 0.008$). High intake of total fat was associated with non-significant decrease in the risk ($P = 0.12$), while high intake of SFA resulted in statistically non-significant increase in risk ($P = 0.40$). Significant reductions in risk were associated with high frequencies of consumption of vegetables ($P = 0.001$) and fruit ($P = 0.009$). There were results suggestive of a decreased risk with a high frequency of milk consumption ($P = 0.06$) and an increased risk in association with a ratio of meat to vegetable frequencies ($P = 0.09$). After adjustment among factors effecting risk of colorectal cancer statistically significant increase in the risk was seen only for protein/cellulose ratio and significant protective effect for PUFA/SFA ratio, beta-carotene and vegetable consumption.
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INTRODUCTION

INCIDENCE OF large bowel cancer in Russia as a whole is lower than in Western Europe and North America [1]. Age-standardised incidence rates (world standard population) for colon cancer in 1989 were 11.2 in men and 9.0 in women and rectal cancer 11.1 in men and 7.7 in women [2]. Incidence rates for colorectal cancer in Moscow and Chabarovsk, cities where the presented case-control study was carried out are somewhat higher. In Moscow age-standardised incidence rates for colon cancer are 17.6 (men) and 13.4 (women) and for rectal cancer 10.9 (men) and 8.4 (women). In Chabarovsk incidence of colon cancer is 17.0 (men) and 14.7 (women) and rectal cancer 15.8 (men) and 10.0 (women). The incidence rates for colon cancer in Moscow have increased in both males and females since 1971, but the incidence rates of rectal cancer have significantly increased only in males [3].

Diet is suspected to have considerable influence on colorectal cancer risk [4, 5]. The results of several studies indicate that high intakes of fat increase risk of cancer or polyps of the large intestine [6–12]. A high fibre intake has been implicated as a protective factor [10–15]. Because of potential confounding, it is not clear whether these effects operate independently.

There are exceptions to these findings. Martinez *et al.* [16] found an increased risk in association with high fibre intake. Some workers have observed a decreased risk in association with high intakes of polyunsaturated fat [17]. The finding of Macquart-Moulin *et al.* [15] of a reduced risk with a high consumption of vegetable oil is consistent with this.

In several studies an increased risk has been observed in association with high meat consumption or high protein intakes [5, 6, 18, 19]. Lee *et al.* [21] found an increased risk to be related to a high ratio of meat to vegetable intakes. The observed effect of fat may thus be a product of an underlying effect of a component of fat such as saturated fats or of a correlate such as animal protein.

Evidence on the presence of an increased risk conferred by drinking alcohol is not conclusive [21, 22], although such an effect has been observed in some studies, notably for high beer consumption [23, 24].

In this paper we report the results of combined analysis of two case-control studies of colorectal cancer and diet, one in Moscow and one in Khabarovsk, in the far east of Russia.

PATIENTS AND METHODS

The Moscow study comprised 100 cases of colorectal cancer (45 of colon and 55 of rectum) and 100 neighbourhood controls taken from persons attending, for minor complaints only, the same regional outpatient clinic as the patients with colorectal cancer. Neighbourhoods were defined as the catchment areas for local polyclinics, the primary care units in Moscow. A polyclinic typically serves 30 000 people.

Controls were matched for age, sex and history of heart disease. The last matching factor was necessary as there was a possibility that heart disease patients would be over-represented in the controls, and that some dietary risk factors of the two diseases would coincide. All cases and controls resided in the city of Moscow.

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Table 1. Cut points for four categories of nutrient intakes based on joint control group (joint analysis of Moscow and Khabarovsk)

Nutrient	Male	Female
Protein (g)	94.1, 118.5, 137.8	79.7, 110.4, 140.0
Total fat (g)	134.7, 176.5, 222.1	124.5, 165.8, 209.6
Cholesterol (g)	0.7, 1.0, 1.4	0.6, 0.9, 1.2
SFA* (g)	48.3, 65.2, 80.8	44.5, 60.4, 74.8
MUFA† (g)	45.9, 58.2, 72.4	42.8, 57.7, 69.4
PUFA‡ (g)	15.1, 20.41, 30.4	17.0, 23.3, 31.2
Mono-Disaccharides (g)	73.0, 107.4, 152.0	88.7, 120.8, 176.9
Starch (g)	128.3, 157.6, 216.2	117.8, 157.1, 204.3
Cellulose (g)	6.1, 7.8, 9.6	6.1, 8.1, 10.4
Vitamin A (mg)	0.6, 0.7, 0.9	0.5, 0.7, 0.8
Beta-carotene (mg)	1.6, 2.0, 2.7	1.6, 2.3, 2.8
Vitamin C (mg)	107.6, 175.3, 253.1	150.3, 224.5, 329.9
K (mg)	3122.4, 3984.0, 4677.7	3117.4, 4077.1, 5111.2
Ca (mg)	749.7, 1138.9, 1477.9	890.4, 1114.3, 1545.1
Mg (mg)	310.3, 384.2, 467.8	311.1, 399.0, 498.6

*Saturated fatty acids.
†Monounsaturated fatty acids.
‡Polyunsaturated fatty acids.

The Khabarovsk study consisted of 117 cases (47 of colon and 70 of rectum) and 117 population controls matched for age and sex, randomly drawn from the local electoral population lists.

All cases in both studies were histology confirmed and classified according to ICD-9 [25]. The higher numbers of rectal cancer in our study, most probably, reflect the clinical (surgical) activity of the hospitals from where the case samples were drawn. The study of descriptive epidemiology of colon and rectal cancer in Moscow has shown, that higher proportion of rectal (85%) than colon cancer (80%) is morphologically verified [3]. The latter suggests that more patients with rectal than with colon cancer are admitted to hospitals or other medical institutions with relevant diagnostic facilities.

Dietary assessment was by a food frequency questionnaire, composed of 132 food items. Foods were converted to nutrient intakes using food tables compiled for the foods commonly eaten in Russia [26, 27]. Nutrients were not expressed as quantitative daily intakes but categorised into quarters of the control range. Nutrients assessed for effects on risk were protein, total fat, cholesterol, saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA), mono- and disaccharides (MDS), starch, cellulose, vitamin A, beta-carotene, vitamin C, potassium, calcium and magnesium. Broad foods assessed were frequencies of consumption of meat, fish, milk, cabbage and fruit.

Statistical analysis was by conditional logistic regression [28], yielding odds ratio (OR) estimates of relative risk and deviance χ^2 tests for effects of variables on risk, taking the matched design into account. All analyses were adjusted for educational status (as a measure of socioeconomic status) and total energy intake. Adjustment for these variables was by their inclusion in the logistic regression model [29]. Data were analysed firstly for each study separately, dividing the ranges using the control quartiles specific to each study, then for both studies together, using quartiles calculated from the two control groups combined. For some variables and combinations, grouping of the data made it necessary to divide the range into only two or three groups instead of four.

RESULTS

Logistic regression analysis was based on the quartiles of intake of joint control group. The 25%, 50% and 75% cutpoints are shown in Table 1.

Results for the combined analysis, with respect to nutrients are given in Table 2. Significantly reduced risks were observed with high intakes of cellulose ($P = 0.001$), beta-carotene ($P = 0.002$), vitamin C ($P = 0.007$), PUFA ($P = 0.004$), cholesterol ($P = 0.04$), and with a high ratio of PUFA to SFA ($P = 0.002$). Significant increases in risk were observed in association with high ratios of intakes of protein to cellulose ($P = 0.002$) and of fat to cellulose ($P = 0.008$). There was a suggestive reduction in risk with high potassium intakes. High intake of total fat was associated with non-significant decrease in the risk ($P = 0.12$), while high intake of SFA resulted in statistically non-significant increase in risk ($P = 0.40$).

Results of both studies combined for food groups are shown in Table 3. Significant reductions in risk were associated with high frequencies of consumption of total vegetables ($P = 0.001$) and fruits ($P = 0.009$). Suggestive results were a decreased risk with a high frequency of milk consumption ($P = 0.06$) and an increased risk in association with a ratio of meat to vegetable frequencies ($P = 0.09$).

Whilst not wishing to over-analyse these data with complex multivariate and stepwise models, we did analyse three adjusted models from the variables found to have significant effects (detailed results available from the authors): the high energy variables (cholesterol, PUFA, PUFA to SFA ratio, cellulose, protein to cellulose ratio and fat to cellulose ratio) adjusted for each other; the vitamins (beta-carotene and vitamin C) adjusted for each other; and the frequencies of fruit and vegetables adjusted for each other. The effects of cholesterol, PUFA, cellulose, and fat to cellulose ratio lost their significance when adjusted for the ratios of PUFA to SFA and protein to cellulose. The effect of vitamin C lost its significance when adjusted for beta-carotene. The effect of frequency of fruit consumption lost its significance when adjusted for frequency of consumption of vegetables. Thus after adjustment among factors effecting risk of colorectal cancer statistically significant increase in the risk was seen only for protein/cellulose ratio and significant protective effect for PUFA/SFA ratio, beta-carotene and vegetable consumption.

DISCUSSION

The major results of the study are reduced risks in association with high beta-carotene intake, high vegetable consumption and a high ratio of PUFA to SFA intakes, and an increased risk in association with a high protein to cellulose ratio. Significant results in related variables were reduced risks with high consumption of cholesterol, PUFA, cellulose, vitamin C and fruit, and increased risks in association with a high fat to cellulose ratio.

Clearly there are strong correlations among these variables, and they cannot be expected to operate as predictors of risk independently of each other. There is, nevertheless a clear pattern. If we take the four most consistent predictors, beta-carotene, vegetables, PUFA to SFA ratio and protein to cellulose ratio, the implication is that a diet high in protein and animal fats is likely to predispose to colorectal cancer and a diet high in vegetables and fibre is likely to protect. It also appears likely from these results that PUFA has a protective capability rather than a high PUFA effect being simply a proxy for a low SFA

Table 2. Results of logistic regression analysis of effects of nutrient intakes on risk, for colo-rectal cancer, adjusted for energy intake and education (joint analysis of Moscow and Khabarovsk studies)

Risk factor	Category*	Number Cases	Number Controls	OR adjusted† (95% CL)	P (trend)
Protein	1	38	54	1	
	2	59	54	1.16 (0.56–2.41)	
	3	58	55	0.74 (0.29–1.87)	
	4	62	54	0.75 (0.26–2.15)	0.47
Total fat	1	42	54	1	
	2	57	54	0.83 (0.37–1.84)	
	3	60	54	0.51 (0.17–1.48)	
	4	58	55	0.42 (0.13–1.34)	0.12
Cholesterol	1	53	54	1	
	2	60	53	0.84 (0.44–1.60)	
	3	48	56	0.50 (0.24–1.02)	
	4	56	54	0.50 (0.24–1.06)	0.04
SFA‡	1	33	54	1	
	2	56	54	1.41 (0.72–2.76)	
	3	58	55	1.29 (0.52–3.22)	
	4	70	54	1.56 (0.59–4.18)	0.40
MUFA§	1	44	54	1	
	2	57	55	0.76 (0.37–1.56)	
	3	55	55	0.52 (0.21–1.29)	
	4	61	53	0.54 (0.20–1.51)	0.23
PUFA‖	1	57	54	1	
	2	57	55	0.64 (0.35–1.17)	
	3	63	54	0.56 (0.28–1.13)	
	4	40	54	0.29 (0.13–0.64)	0.004
Mono-disaccharides	1	39	54	1	
	2	52	55	1.11 (0.60–2.10)	
	3	67	54	1.30 (0.62–2.75)	
	4	59	54	1.16 (0.48–2.80)	0.72
Starch	1	34	54	1	
	2	48	54	1.16 (0.57–2.37)	
	3	69	55	1.77 (0.80–3.92)	
	4	66	54	2.01 (0.77–5.24)	0.11
Cellulose	1	64	54	1	
	2	52	52	0.53 (0.28–1.00)	
	3	55	56	0.35 (0.16–0.74)	
	4	46	55	0.26 (0.11–0.58)	0.001
Vitamin A	1	52	56	1	
	2	42	52	0.62 (0.32–1.19)	
	3	58	55	0.61 (0.29–1.28)	
	4	65	54	0.68 (0.29–1.59)	0.41
Beta-carotene	1	75	55	1	
	2	39	53	0.25 (0.12–0.51)	
	3	55	55	0.33 (0.16–0.70)	
	4	48	54	0.21 (0.09–0.48)	0.002
Vitamin C	1	76	54	1	
	2	45	54	0.46 (0.26–0.82)	
	3	54	56	0.50 (0.27–0.92)	
	4	42	53	0.40 (0.21–0.73)	0.007
K	1	53	54	1	
	2	45	55	0.48 (0.23–0.97)	
	3	59	54	0.42 (0.17–1.06)	
	4	60	54	0.39 (0.13–1.17)	0.095
Ca	1	53	54	1	
	2	46	55	0.63 (0.34–1.18)	
	3	62	55	0.62 (0.30–1.29)	
	4	56	53	0.52 (0.24–1.13)	0.13
Mg	1	46	55	1	
	2	43	54	0.68 (0.34–1.36)	
	3	64	53	0.78 (0.31–1.93)	
	4	64	55	0.78 (0.27–2.26)	0.67
Ratio PUFA/SFA	1	96	60	1	
	2	43	51	0.53 (0.30–0.93)	
	3	46	56	0.54 (0.32–0.89)	
	4	32	50	0.37 (0.20–0.69)	0.002
Ratio protein/cellulose	1	41	59	1	
	2	37	50	0.96 (0.53–1.75)	
	3	48	54	1.26 (0.70–2.28)	
	4	91	54	2.35 (1.31–4.21)	0.002
Ratio fat/cellulose	1	31	54	1	
	2	46	56	1.29 (0.70–2.38)	
	3	72	53	2.52 (1.31–4.86)	
	4	68	54	2.10 (1.11–3.97)	0.008

*Categories on the base of joint control group.
†Odds ratio adjusted for energy intake and education.
‡Saturated fatty acids.
§Monounsaturated fatty acids.
‖Polyunsaturated fatty acids.

effect. This also suggests that a reduction of total fat alone is not sufficient to reduce risk of this disease.

These results are not in agreement with those studies which find total fat or total fibre to be the important predictors of this disease [5, 8, 9]. They do, however, add further credibility to the findings of some workers that relative intakes are of importance [12, 13, 20, 21]. It is certainly biologically reasonable to consider high- and low-risk overall dietary patterns. We did not identify an association between risk of colorectal cancer and protein, meat and total fat until undertaking an analysis of each of these nutrients in conjunction with the cellulose consumption. Like Dales *et al.* [13], and partly Graham *et al.* [10] we found that when fat was examined in combination with fibre the risk of colorectal cancer increased with increasing ratio of consumption fat to cellulose. The effect of protein to cellulose ratio on the risk of colorectal cancer observed in this study is in agreement with previous studies [20, 21]. Moreover in one of these studies [20], major differences in colorectal cancer risk were seen between high-meat, low-vegetable (high-risk) and low-meat, high-vegetable (low-risk) diets.

The present results suggest a protective role of beta-carotene and vitamin-C against colo-rectal cancer. For vitamin A, however, the effect was absent. No association was evident between retinol and cancers of the colon and rectum by a case-control

Table 3. Results of logistic regression analysis of effects of food intakes on risk, for colo-rectal cancer, adjusted for energy intake and education (joint analysis of Moscow and Khabarovsk studies)

Risk factor	Category*	No. of cases	No. of controls	OR Adjusted† (95% CL)		P (trend)
Meat	1	55	51	1		
	2	56	49	0.84	(0.47–1.50)	
	3	55	54	0.88	(0.48–1.61)	
	4	51	63	1.02	(0.54–1.96)	0.87
Milk	1	57	53	1		
	2	53	61	1.28	(0.72–2.27)	
	3	54	58	0.86	(0.47–1.55)	
	4	53	45	0.53	(0.27–1.03)	0.06
Total vegetables	1	56	81	1		
	2	53	42	0.34	(0.18–0.67)	
	3	54	50	0.37	(0.19–0.72)	
	4	54	44	0.27	(0.13–0.57)	0.001
Ratio meat/vegetables	1	57	56	1		
	2	54	39	0.74	(0.43–1.27)	
	3	53	40	0.76	(0.44–1.30)	
	4	53	82	1.97	(1.08–3.58)	0.09
Cabbage	1	54	56	1		
	2	55	41	0.64	(0.36–1.16)	
	3	54	56	0.85	(0.45–1.63)	
	4	54	64	1.04	(0.53–2.01)	0.68
Fruits	1	55	71	1		
	2	54	58	0.72	(0.42–1.24)	
	3	54	50	0.54	(0.30–0.97)	
	4	54	38	0.47	(0.26–0.86)	0.009
Fish	1	67	53	1		
	2	46	51	1.27	(0.73–2.22)	
	3	55	67	1.34	(0.76–2.38)	
	4	49	46	0.99	(0.52–1.89)	0.91

*Categories on the base of joint control group.
†Odds ratio adjusted for energy intake and education.

study in a northern Italian population, but relative risk were inversely related with carotenoids and vitamin C intake. The mildly protective role of beta-carotene against colorectal cancer was shown by case-control study in Singapore [21]. On the other hand Potter and McMichael [30] did not observe an effect of beta-carotene on the risk of colorectal cancer. Our results are also consistent with findings that polyunsaturates and correlates there of, actually have a protective effect [14–16]. Similar results have been observed in the breast cancer case-control study carried out in Moscow [31].

In conclusion, our principal results are that a diet high in vegetables, fruit, cellulose, vitamins and polyunsaturates is associated with a low risk of colorectal cancer and one high in proteins and saturated fats relative to the more beneficial dietary components is associated with high risk.

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