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Diet and risk of colorectal cancer in a cohort of Finnish men

Pirjo Pietinen[1,*], Nea Malila[1], Mikko Virtanen[1], Terryl J. Hartman[2], Joseph A. Tangrea[2], Demetrius Albanes[2] & Jarmo Virtamo[1]
[1]*Department of Nutrition, National Public Health Institute, Manerheimintie 166, 00300 Helsinki, Finland;* [2]*Division of Clinical Sciences, National Cancer Institute, CIH, Bethesda, MD, USA (*Author for correspondence)*

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Abstract

Objectives: Based on previous epidemiological studies, high fat and meat consumption may increase and fiber, calcium, and vegetable consumption may decrease the risk of colorectal cancer. We sought to address these hypotheses in a male Finnish cohort.
Methods: We analyzed data from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study) where 27, 111 male smokers completed a validated dietary questionnaire at baseline. After an average of 8 years of follow-up, we documented 185 cases of colorectal cancer. The analyses were carried out using the Cox proportional hazards model.
Results: The relative risk (RR) for men in the highest quartile of calcium intake compared with men in the lowest quartile was 0.6 (95% CI 0.4–0.9, p for trend 0.04). Likewise, the intake of milk protein and the consumption of milk products was inversely associated with risk of colorectal cancer. However, intake of dietary fiber was not associated with risk, nor was fat intake. Consumption of meat or different types of meat, and fried meat, fruits or vegetables were not associated with risk.
Conclusions: In this cohort of men consuming a diet high in fat, meat, and fiber and low in vegetables, high calcium intake was associated with lowered risk of colorectal cancer.

Introduction

Rates of colorectal cancer vary tremendously between countries [1] showing that even though a genetic component is well established [2], environmental factors seem to be strongly related to risk of colorectal cancer. Two of the main hypotheses concerning the role of diet have been that fat and meat consumption may increase and fiber and vegetable consumption decrease the risk of colon cancer. Between-country comparisons as well as most of the case–control studies support these hypotheses. However, prospective studies have found conflicting results [3]. The protective role of calcium is not supported by strong epidemiological evidence either [4, 5].

Compared internationally, Finland has low colon cancer rates in both genders. This has been thought to be explained mainly by high fiber intake. We examined the associations between several dietary factors and the incidence of colorectal cancer during an average of 8 years of follow-up in a large cohort of Finnish men. We have reported previously that in this cohort alcohol intake increased [6] and low folate intake combined with high alcohol and low protein intake increased the risk of colorectal cancer [7]. Serum vitamin 25-OH D was also inversely associated with risk [8].

Material and methods

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC) was a randomized, double-blind, placebo-controlled primary prevention trial undertaken to determine whether supplementation with alpha-tocopherol, beta-carotene, or both would reduce the

incidence of lung cancer in male smokers. The rationale, design and methods of the study have been previously described in detail [9]. The ATBC Study was approved by the institutional review groups of both the US National Cancer Institute and the National Public Health Institute of Finland.

Participants were male smokers who were 50–69 years of age at entry. They were recruited from the total male population of this age group in southwestern Finland (n = 290,406). To be eligible, the men had to smoke at least five cigarettes per day and to give written consent. The exclusion criteria that would limit participation included history of cancer or other serious disease, the use of vitamin E, vitamin A, or beta-carotene supplements in excess of predefined doses, and treatment with anticoagulant agents. After these exclusions, 29,133 men were randomized into four supplementation regimens: alpha-tocopherol (50 mg/d), beta-carotene (20 mg/d), both or placebo. The trial ended on 30 April 1993. However, the follow-up of cancers and deaths continues, and the follow-up time completed for the analyses of this paper cover the time period until 30 April 1995 (on average 8 years).

Diet was assessed at baseline using a self-administered modified dietary history method [10]. This questionnaire was satisfactorily completed by 27,111 (93%) participants. At baseline, the men also provided information on general characteristics and medical, smoking and occupational history. Educational level was categorized as <7 years of school, 7 to 11 years, or >11 years. Occupational physical activity was categorized into four groups starting from sedentary work. Height and weight were measured, and body mass index was calculated as weight (kg) divided by height squared (m^2).

Dietary assessment

The diet questionnaire included 276 food items and mixed dishes and a portion size picture booklet of 122 photographs of foods, each with 3–5 different portion sizes. The subjects were asked to report the usual frequency of consumption and the usual portion size of foods during the previous 12 months. At baseline, the questionnaire together with the picture booklet was given to the subject to be completed at home and it was returned and checked by a study nurse two weeks later. The food consumption data were processed using the software and food composition database at the National Public Health Institute. The fatty acid content as well as the fiber content of foods are based on analyses carried out at the Department of Food Chemistry, University of Helsinki. The fatty acid database contains 77 individual fatty acids or fatty acid isomers. The fiber content of foods was analyzed by the Englyst method which measured the total carbohydrate composition as the following fractions: soluble sugars, starch, and dietary fiber as cellulose; water-soluble and water-insoluble noncellulosic polysaccharides; and lignin [11]. In addition to these chemically different fiber fractions, we separately calculated total dietary fiber from cereals, vegetables, and fruit.

A fried meat variable was constructed by adding up the frequency of use of all dishes where the meat is prepared by frying (fried and grilled steaks, pork chops etc., altogether 15 foods). In a similar manner, we added up all breads, porridges and whole-grain breakfast cereals (altogether 17 items) which consist of at least partly whole grain and called this a whole grain variable. The consumption of cruciferous vegetables was a sum of 11 food items where the Brassica vegetables (cauliflower, cabbage, broccoli, brussels sprouts) were eaten either alone or as the main ingredient of a dish. We carried out the analyses with the whole grain variable and the cruciferous vegetable variable both as frequency per year and as amount in grams.

Based on the validation study of the dietary method carried out prior to the trial [10], the correlations between the questionnaire-based, energy-adjusted intakes and those based on 24 days of food recording were 0.52 for total fat, 0.73 for dietary fiber, and 0.66 for calcium.

Case identification

The cases were defined as all incident cases of colon cancer (ICD-9 code 153-, n = 114) and rectal cancer (ICD-9 code 154-, n = 86) diagnosed between randomization and 30 April 1995, and identified through the Finnish Cancer Registry. Malignant carcinoids (n = 3) and anal canal cancer (n = 3) have been excluded as well as 9 cases with no dietary information, leaving a total of 185 cases for analyses. All cases were reviewed centrally by two oncologists and a pathologist checked the original histological specimens. In cases of multiple colorectal cancers, the first one was chosen (n = 2), and when the tumors were diagnosed simultaneously, the most invasive one was chosen (n = 2). In one case with three simultaneous colorectal cancers, the data were combined, and the ICD-9 code not indicating a specific site within the colon was used.

Statistical analyses

The men contributed follow-up time from the date of randomization until diagnosis of colorectal cancer, death, or 30 April 1995. Men were grouped in quartiles of energy-adjusted intakes of nutrients or foods as

calculated from the dietary questionnaire. All nutrients were log-transformed before the energy adjustment, which was done by the residual method [12].

Proportional hazards models were used to estimate the relative risks (with 95% confidence interval) of colorectal cancer associated with intakes of nutrients and foods, with simultaneous adjustment for age and supplement group first (base model). Adjustment for supplement group was done since the main results of the trial showed that there were fewer cases of colorectal cancer in the groups supplemented with alpha-tocopherol [13]. In the multivariate model, further adjustment was made for smoking years (< 35 or over), body mass index (tertiles), alcohol consumption (tertiles), education, occupational physical activity, and calcium intake. The significance of trend was tested *post hoc* from the fitted models using Wald test with a linear contrast. The analyses were also redone excluding all cases from the first two years of follow-up, but this did not alter the results. The validity of the underlying proportional hazards assumption was studied using methods described by Grambsch and Therneau [14].

Table 1. Background characteristics and energy-adjusted intakes of nutrients and foods in cases of colorectal cancer and in noncases

Variable	Cases n = 185	Noncases n = 26,926
Medians of		
Age (years)	60.1	57.1
Smoking (years)	39.3	36.4
BMI (kg/m^2)	26.3	26.0
% of group		
Education (> 11 years)	10.8	10.0
Physical activity (moderate)	13.9	25.8
Median daily intake of		
Energy (kcal)	2731	2720
Total protein (g)	98	100
Total triglycerides (g)	100	101
Saturated fatty acids (g)	47.8	50.0
Monounsaturated fatty acids (g)	35.2	35.0
Polyunsaturated fatty acids (g)	10.2	9.6
Trans fatty acids (g)	3.0	2.9
Dietary fiber (g)	24.6	24.2
Calcium (mg)	1286	1338
Vitamin D (mg)	4.8	4.8
Alcohol (g)	9.6	11.2
Median daily consumption of		
Milk products (g)	684	735
Whole grain products (g)	216	212
Vegetables (g)	103	99
Cruciferous vegetables (g)	16.1	12.8
Fruit (g)	111	103
Red meat (g)	125	128

Results

The colorectal cancer cases were older, had a higher body mass index and had smoked for a longer time period than the noncases (Table 1). They were also better educated but less physically active than the others. Their daily intake of calcium as well as milk products was lower and the consumption of cruciferous vegetables was higher compared to the others.

Energy intake was not related to risk of colorectal cancer either in the base model or in the multivariate model, adjusting further for smoking years, body mass index, alcohol, education, and physical activity at work (Table 2). However, after additional adjustment for calcium, energy intake was related to increased risk, the relative risk in the highest quartile of intake being 1.7 (95% CI 1.0–2.9, p for trend 0.05). Intakes of total protein or meat or vegetable proteins were not associated with risk of colorectal cancer. Intakes of milk protein and calcium were found to have a strong inverse association with risk of colorectal cancer. The relative risk in men in the highest quartile of calcium intake compared to the lowest was 0.6 (95% CI 0.4–0.9, p for trend 0.04). The result did not change in the multivariate model. The apparently protective effect of calcium was seen already in the second quartile of intake. The results were almost identical when calcium from supplements was added to dietary calcium. Only 11% of the men used calcium supplements. High consumption of milk products lowered the risk, which is in line with the results on calcium intake. Consumption of sour milk products was, however, not related to risk of colorectal cancer, neither was intake of vitamin D.

Intake of total fat was not associated with risk of colorectal cancer (Table 3). Intake of saturated fatty acids had a significant inverse association with risk of colorectal cancer in the base model, but the association was attenuated in the multivariate model. Intakes of total polyunsaturated fatty acids as well as of linoleic and linolenic acids seemed to be directly related to the risk of colorectal cancer in the base model, but the associations were attenuated in the multivariate model. Intakes of cis-monounsaturated fatty acids, trans-fatty acids, omega-3 fish fatty acids or cholesterol were not associated with risk of colorectal cancer. Mutual adjustment for each other did not change the results on saturated, monounsaturated and polyunsaturated fatty acids, and neither did further adjustment for dietary fiber.

There were no associations between risk of colorectal cancer and intakes of total dietary fiber, soluble or insoluble fiber or fiber from rye products, which are the

Table 2. Relative risk of colorectal cancer by quartiles of energy and energy-adjusted daily intakes of calcium, protein vitamin D and milk products

	Quartile group, medians of intake				*p* for trend
	1	2	3	4	
Total energy (kcal)	1984	2495	2969	3696	
Number of cases	40	52	51	42	
Age-adjusted RR* (95% CI)	1.0	1.4 (0.9–2.1)	1.4 (0.9–2.1)	1.2 (0.8–1.9)	0.42
Multivariate RR** (95% CI)	1.0	1.5 (1.0–2.4)	1.7 (1.1–2.7)	1.7 (1.0–2.9)	0.05
Total protein (g)	83.8	96.9	105.1	115.9	
Number of cases	52	54	41	38	
Age-adjusted RR* (95% CI)	1.0	1.1 (0.7–1.5)	0.8 (0.5–1.2)	0.8 (0.5–1.2)	0.13
Multivariate RR** (95%CI)	1.0	1.2 (0.8–1.7)	0.9 (0.6–1.4)	0.9 (0.5–1.5)	0.47
Milk protein (g)	16.3	27.6	34.8	43.6	
Number of cases	57	46	46	36	
Age-adjusted RR* (95% CI)	1.0	0.8 (0.5–1.26)	0.8 (0.5–1.1)	0.6 (0.4–0.9)	0.02
Multivariate RR** (95% CI)	1.0	0.8 (0.5–1.2)	0.8 (0.5–1.1)	0.6 (0.4–0.9)	0.02
Meat protein (g)	25.3	33.7	41.0	53.6	
Number of cases	45	50	51	39	
Age-adjusted RR* (95% CI)	1.0	1.2 (0.8–1.7)	1.2 (0.8–1.9)	1.0 (0.7–1.5)	0.90
Multivariate RR** (95% CI)	1.0	1.1 (0.7–1.7)	1.2 (0.8–1.8)	0.9 (0.6–1.4)	0.68
Vegetable protein (g)	22.5	28.8	32.8	38.8	
Number of cases	33	45	58	49	
Age-adjusted RR* (95% CI)	1.0	1.3 (0.9–2.1)	1.7 (1.1–2.6)	1.4 (0.9–2.2)	0.08
Multivariate RR** (95% CI)	1.0	1.3 (0.8–2.1)	1.7 (1.1–2.6)	1.3 (0.8–2.1)	0.16
Calcium (mg)	856	1241	1484	1789	
Number of cases	60	41	45	39	
Age-adjusted RR* (95% CI)	1.0	0.7 (0.4–1.0)	0.7 (0.5–1.1)	0.6 (0.4–0.9)	0.04
Multivariate RR** (95% CI)	1.0	0.7 (0.5–1.0)	0.7 (0.5–1.1)	0.6 (0.4–0.9)	0.04
Vitamin D (μg)	2.58	4.13	5.71	8.62	
Number of cases	47	46	41	51	
Age-adjusted RR* (95% CI)	1.0	1.0 (0.6–1.5)	0.9 (0.6–1.3)	1.1 (0.7–1.6)	0.86
Multivariate RR** (95% CI)	1.0	1.0 (0.6–1.4)	0.8 (0.5–1.2)	1.0 (0.7–1.5)	0.77
Milk products (g)	318	656	864	1089	
Number of cases	56	49	41	39	
Age-adjusted RR* (95% CI)	1.0	0.7 (0.5–1.0)	0.8 (0.5–1.2)	0.6 (0.4–0.8)	0.01
Multivariate RR** (95% CI)	1.0	0.7 (0.5–1.1)	0.8 (0.5–1.2)	0.6 (0.4–0.9)	0.02
Sour milk products (g)	0	33	168	350	
Number of cases	41	52	44	48	
Age-adjusted RR* (95% CI)	1.0	1.3 (0.9–1.9)	1.1 (0.7–1.6)	1.1 (0.7–1.7)	0.79
Multivariate RR** (95% CI)	1.0	1.3 (0.9–1.9)	1.1 (0.7–1.6)	1.1 (0.7–1.3)	0.87

* Adjusted for age (5-year categories) and supplement group.

** Adjusted further for smoking years, body mass index, alcohol, education, and physical activity at work, and calcium intake (except for milk protein and milk products).

most important sources of fiber in the Finnish diet (Table 4). Intakes of cereal, vegetable or fruit fiber were not associated with the risk of colorectal cancer, neither was starch or sugar (data not shown). Stratification of the subjects into low-fat, high-fiber *vs.* high-fat low-fiber groups did not show any association between fat or fiber intake with risk of colorectal cancer, either (data not shown). There were no associations for consumption of whole grain cereals, rye products, vegetables or fruit, either. Adjustment for calcium or fat intake did not change any of the results. Consumption of cruciferous vegetables was, however, positively related to risk of colorectal cancer, the relative risk in the highest quartile compared to the lowest being 1.6 (95% CI 1.0–2.3, *p* for trend 0.04).

We investigated the possible association between meat intake and risk of colon cancer first by meat groups, beef, lamb and pork together and processed meat

Table 3. Relative risk of colorectal cancer by quartiles of energy-adjusted intakes of different types of fat

	Quartile group, medians of intake				*p* for trend
	1	2	3	4	
Total fat (g)	81.6	97.2	107.2	119.0	
Number of cases	54	44	40	47	
Age-adjusted RR* (95% CI)	1.0	0.8 (0.5–1.2)	0.7 (0.5–1.1)	0.8 (0.5–1.2)	0.21
Multivariate RR** (95% CI)	1.0	0.8 (0.5–1.2)	0.8 (0.6–1.1)	0.9 (0.6–1.3)	0.41
Saturated fatty acids (g)	33.8	45.6	55.2	65.1	
Number of cases	51	54	34	46	
Age-adjusted RR* (95% CI)	1.0	1.0 (0.7–1.5)	0.6 (0.4–0.9)	0.8 (0.5–1.2)	0.05
Multivariate RR** (95% CI)	1.0	1.1 (0.8–1.6)	0.7 (0.45–1.1)	0.9 (0.6–1.4)	0.27
Monounsaturated f.a. (g)	28.4	33.9	37.1	40.7	
Number of cases	48	42	40	55	
Age-adjusted RR* (95% CI)	1.0	0.9 (0.6–1.3)	0.9 (0.6–1.3)	1.2 (0.8–1.8)	0.41
Multivariate RR** (95% CI)	1.0	0.9 (0.6–1.4)	0.9 (0.6–1.3)	1.2 (0.8–1.8)	0.44
Polyunsaturated f.a. (g)	6.5	8.7	11.5	19.4	
Number of cases	39	47	44	55	
Age-adjusted RR* (95% CI)	1.0	1.3 (0.8–2.0)	1.3 (0.8–2.0)	1.6 (1.0–2.4)	0.04
Multivariate RR** (95% CI)	1.0	1.2 (0.8–1.9)	1.2 (0.7–1.8)	1.4 (0.9–2.1)	0.18
Trans fatty acids (g)	1.8	2.6	3.4	5.7	
Number of cases	47	38	46	54	
Age-adjusted RR* (95% CI)	1.0	0.8 (0.5–1.2)	0.9 (0.6–1.3)	1.1 (0.8–1.6)	0.44
Multivariate RR** (95% CI)	1.0	0.8 (0.5–1.2)	0.9 (0.6–1.4)	1.1 (0.7–1.6)	0.49
Linoleic acid (g)	4.5	6.1	8.5	16.4	
Number of cases	41	43	48	53	
Age-adjusted RR* (95% CI)	1.0	1.1 (0.7–1.7)	1.3 (0.9–2.0)	1.4 (1.0–2.2)	0.05
Multivariate RR** (95% CI)	1.0	1.1 (0.7–1.7)	1.2 (0.8–1.9)	1.3 (0.8–2.0)	0.20
Linolenic acid (g)	1.0	1.4	1.8	2.4	
Number of cases	41	43	48	53	
Age-adjusted RR* (95%CI)	1.0	1.3 (0.9–2.1)	1.4 (0.9–2.2)	1.6 (1.0–2.4)	0.04
Multivariate RR** (95% CI)	1.0	1.3 (0.8–2.0)	1.3 (0.8–2.0)	1.4 (0.9–2.1)	0.17
Omega-3 fish fatty acids (g)	0.2	0.3	0.5	0.7	
Number of cases	36	62	41	46	
Age-adjusted RR* (95%CI)	1.0	1.7 (1.1–2.6)	1.2 (0.7–1.8)	1.3 (0.9–2.1)	0.51
Multivariate RR** (95% CI)	1.0	1.7 (1.1–2.5)	1.1 (0.7–1.7)	1.2 (0.8–1.9)	0.84
Cholesterol (mg)	378	501	594	759	
Number of cases	43	48	52	42	
Age-adjusted RR* (95% CI)	1.0	1.2 (0.7–1.7)	1.2 (0.8–1.8)	1.0 (0.6–1.5)	0.92
Multivariate RR** (95% CI)	1.0	1.2 (0.8–1.8)	1.1 (0.8–1.9)	1.0 (0.7–1.6)	0.77

* Adjusted for age (5-year categories) and supplement group.
** Adjusted further for smoking years, body mass index, alcohol, education, physical activity at work, and calcium intake.

separately and then combined them as total red meat consumption. None of these was associated with risk of colorectal cancer (Table 5). Again, since multivariate adjustment did not change the results, only the base model adjusting for age and supplement group is shown. Consumption of poultry or fish was not associated with risk of colorectal cancer, either. We also constructed a meat/poultry plus fish ratio by simply using the amounts consumed. There was no difference in risk among men eating mostly red meat compared to those eating mostly fish and chicken. The frequency of eating fried meat, which varied from on average twice a month in the lowest quartile to about four times a week in the highest quartile, also showed a null association with risk of colorectal cancer.

Discussion

The results of this study are quite surprising. Intakes of fat or fiber were not related to risk of colorectal cancer, and neither was consumption of meat, vegetables, or

Table 4. Relative risk of colorectal cancer by quartiles of energy-adjusted intake of dietary fiber and sources of fiber

	Quartile group, medians of intake				*p* for trend
	1	2	3	4	
Dietary fiber (g)	16.0	22.2	26.9	34.1	
Number of cases	44	48	47	46	
Age-adjusted RR* (95% CI)	1.0	1.1 (0.7–1.6)	1.0 (0.7–1.5)	1.0 (0.7–1.5)	0.93
Multivariate RR** (95% CI)	1.0	1.0 (0.7–1.6)	1.0 (0.7–1.5)	1.0 (0.6–1.5)	0.79
Soluble fiber (g)	3.7	5.0	5.9	7.3	
Number of cases	43	47	44	51	
Age-adjusted RR** (95% CI)	1.0	1.1 (0.7–1.6)	1.0 (0.6–1.5)	1.1 (0.8–1.7)	0.67
Multivariate RR** (95% CI)	1.0	1.0 (0.7–1.6)	1.0 (0.6–1.5)	1.1 (0.7–1.6)	0.91
Insoluble fiber (g)	12.2	17.2	21.0	27.1	
Number of cases	42	52	47	44	
Age-adjusted RR* (95% CI)	1.0	1.2 (0.8–1.8)	1.1 (0.7–1.6)	1.0 (0.7–1.5)	0.84
Multivariate RR** (95% CI)	1.0	1.2 (0.8–1.8)	1.1 (0.7–1.6)	1.0 (0.6–1.5)	0.73
Whole grain cereals (g)	96	181	256	374	
Number of cases	40	49	50	46	
Age-adjusted RR* (95% CI)	1.0	1.2 (0.8–1.8)	1.2 (0.8–1.8)	1.0 (0.7–1.6)	0.93
Multivariate RR** (95% CI)	1.0	1.2 (0.8–1.9)	1.2 (0.8–1.8)	1.0 (0.7–1.6)	0.99
Rye products (g)	23	66	102	157	
Number of cases	53	43	49	40	
Age-adjusted RR** (95% CI)	1.0	0.8 (0.5–1.2)	0.9 (0.6–1.3)	0.7 (0.5–1.1)	0.23
Multivariate RR** (95% CI)	1.0	0.8 (0.5–1.2)	0.9 (0.6–1.4)	0.7 (0.5–1.1)	0.22
Vegetables (g)	44	81	120	191	
Number of cases	39	51	244	51	
Age-adjusted RR* (95% CI)	1.0	1.3 (0.9–2.0)	1.1 (0.7–1.8)	1.3 (0.9–2.0)	0.27
Multivariate RR** (95% CI)	1.0	1.3 (0.8–1.9)	1.1 (0.7–1.7)	1.2 (0.8–1.9)	0.46
Fruit (g)	30	82	132	216	
Number of cases	44	43	42	56	
Age-adjusted RR* (95% CI)	1.0	1.0 (0.6–1.4)	0.9 (0.6–1.4)	1.2 (0.8–1.7)	0.50
Multivariate RR** (95% CI)	1.0	1.0 (0.6–1.4)	0.9 (0.6–1.4)	1.1 (0.8–1.7)	0.64
Cruciferous vegetables (g)	0	8	19	39	
Number of cases	37	42	44	62	
Age-adjusted RR* (95% CI)	1.0	1.1 (0.7–1.8)	1.2 (0.8–1.8)	1.6 (1.1–2.4)	0.03
Multivariate RR** (95% CI)	1.0	1.1 (0.7–1.8)	1.2 (0.8–1.8)	1.6 (1.0–2.3)	0.04

* Adjusted for age (5-year categories) and supplement group.

** Adjusted further for smoking years, body mass index, alcohol, education, physical activity at work, and calcium intake.

whole grain cereals. Instead, calcium intake turned out to be the strongest dietary factor related to colorectal cancer. Consumption of cruciferous vegetables seemed to increase risk which is opposite to the overall epidemiological evidence.

At least nine cohort studies [15–23] have examined the association between calcium and colorectal cancer. A statistically significant inverse association between calcium intake and risk of colorectal cancer was found only in the Western Electric Study [15]. Our study population differs from all the previous studies with its very high calcium intake because of exceptionally high consumption of dairy products, mainly milk. The fact that the relative risk started to decrease already at the second quartile level corresponding to over 1000 mg of calcium indicates that the apparently protective effect of calcium may be shown only at very high levels of intake which are not often found in other populations. Those previous prospective studies which have found suggestive or statistically significant evidence on the protective role of calcium have been carried out in populations where the intake of calcium has also been high [15, 19, 23]. The Western Electric Study was made up of males with presumably high smoking rates given the time of the study. This similarity with our cohort suggests that calcium and milk products may be more important among smokers than nonsmokers.

The mechanism suggested to explain the protective effect of calcium and vitamin D against colorectal cancer involves both the binding of bile acids and fatty acids to

Table 5. Relative risk of colorectal cancer by quartiles of meat, chicken and fish intake

	Quartile group, medians of intake				*p* for trend
	1	2	3	4	
Beef, pork, lamb (g)	35	52	69	99	
Number of cases	55	35	50	45	
Age-adjusted RR* (95% CI)	1.0	0.6 (0.4–1.0)	0.9 (0.6–1.4)	0.9 (0.6–1.3)	0.99
Multivariate RR** (95% CI)	1.0	0.6 (0.4–1.0)	0.9 (0.6–1.3)	0.8 (0.5–1.2)	0.74
Processed meat (g)	26	50	73	122	
Number of cases	41	58	44	42	
Age-adjusted RR* (95% CI)	1.0	1.5 (1.0–2.2)	1.2 (0.8–1.8)	1.2 (0.8–1.8)	0.64
Multivariate RR** (95% CI)	1.0	1.5 (1.0–2.2)	1.1 (0.7–1.8)	1.2 (0.7–1.8)	0.78
Total red meat (g)	79	114	143	203	
Number of cases	46	50	44	45	
Age-adjusted RR* (95% CI)	1.0	1.2 (0.8–1.7)	1.1 (0.7–1.6)	1.2 (0.8–1.8)	0.51
Multivariate RR** (95% CI)	1.0	1.1 (0.8–1.7)	1.0 (0.7–1.6)	1.1 (0.7–1.7)	0.73
Poultry (g)	0	6	13	27	
Number of cases	40	48	47	50	
Age-adjusted RR* (95% CI)	1.0	1.2 (0.8–1.8)	1.2 (0.8–1.9)	1.3 (0.9–2.0)	0.17
Multivariate RR** (95% CI)	1.0	1.1 (0.7–1.7)	1.2 (0.8–1.8)	1.2 (0.8–1.8)	0.40
Fish (g)	13	26	40	68	
Number of cases	46	51	40	48	
Age-adjusted RR* (95% CI)	1.0	1.1 (0.7–1.6)	0.9 (0.6–1.3)	1.0 (0.7–1.5)	0.78
Multivariate RR** (95% CI)	1.0	1.1 (0.7–1.6)	0.8 (0.5–1.3)	0.9 (0.6–1.4)	0.52
Ratio of meat/(poultry + fish)	1.3	2.3	3.6	7.4	
Number of cases	48	47	46	44	
Age-adjusted RR* (95% CI)	1.0	1.0 (0.7–1.5)	1.0 (0.7–1.5)	1.0 (0.7–1.5)	0.93
Multivariate RR** (95% CI)	1.0	1.1 (0.7–1.6)	1.0 (0.7–1.5)	1.1 (0.7–1.6)	0.81
Fried meat, frequency per year	60	108	144	204	
Number of cases	53	51	36	45	
Age-adjusted RR* (95% CI)	1.0	1.0 (0.7–1.4)	0.7 (0.4–1.0)	0.9 (0.6–1.3)	0.27
Multivariate RR** (95% CI)	1.0	1.0 (0.7–1.4)	0.7 (0.4–1.0)	0.9 (0.6–1.3)	0.25

* Adjusted for age (5-year categories) and supplement group.
** Adjusted further for smoking years, body mass index, alcohol, education, physical activity at work, and calcium intake.

form inert soaps, and direct effects on the cell cycle resulting in reduced proliferation and increased terminal differentiation of the colonic epithelial cells [24, 25]. The very high intake of dairy products in our population could, in theory, offer enough calcium to bind the bile acids in this population consuming a high-fat diet.

Milk protein as well as milk products were inversely associated with colorectal cancer. The high correlations between calcium and milk protein (0.98) and between calcium and milk products (0.90) make it, however, difficult to definitely assess the protective compound in milk. Even though we favor the calcium hypothesis, the possibility of casein being a protective factor cannot be ruled out, since there is some evidence from *in vivo* studies that casein has antimutagenic activity over the whole digestive tract except in the stomach [26].

Of the five prospective studies that have reported the association between fat intake and colorectal cancer, only one [27] reported a positive association with total fat and the other five found no association [23, 28–30]. A combined meta-analysis of 13 case–control studies of colorectal cancer found no association with fat intake [31]. None of the prospective studies or the meta-analysis of the case–control studies shows any associations between different types of fat and colorectal cancer. The results of our study are in line with the previous data. Our study is, however, the first one to report on specific fatty acids.

Our finding of no relation between the intake of dietary fiber and risk of colon cancer is consistent with several prospective studies. Even though the meta-analysis of case–control studies showed an inverse association between fiber intake and colorectal cancer [32], the prospective studies have either found no association [23, 27, 29, 33] or a weak positive association [34, 35]. The absence of an association in our study cannot be due to a limited range of intake since the median intake of fiber was 16 g in the lowest quartile

and 34 g in the highest quartile. A strong inverse association between fiber intake and coronary death was found in this same cohort [37] indicating that we had a physiologically relevant measure of fiber intake. It should be noted, however, that the whole range is in the high end of intake compared with other populations. A recent case–control study found that the protective effect of dietary fiber was to a large extent due to fiber from vegetables, since no clear association was found with fiber from cereals or fruits [38]. In our population, the intake of vegetable fiber was about the same as in this Hawaian study, from 3 to 6 g, yet we found no association.

In contrast to the general belief at the moment, consumption of whole grain cereals, vegetables, or fruit was not found to be protective of colorectal cancer. To show that the results cannot be a consequence of poor measurement, we refer to our previous finding which showed that high consumption of rye products (the main source of fiber), vegetables and fruit was associated with lowered risk of coronary heart disease [37]. However, at the time of those analyses we had not constructed the whole grain variable yet. It shows that all our subjects consume whole grain cereals daily, which, again, makes our study population exceptional. A review of studies which have reported the association between whole grain intake and risk of colorectal cancer has shown an inverse association in populations where whole grain intake was lower than ours [39]. High consumption of rye could, in theory, protect against breast, prostate and colorectal cancers because of its high content of lignans [40, 41]. We could not, however, find any support to this phytoestrogen theory from our results. For cruciferous vegetables, 8 of 12 studies have shown decreased risks with higher consumption and findings from the three remaining four studies were null [42]. Thus, our finding of increased risk with higher consumption could be a chance finding. The consumption level was very low in our population, the median in the highest quartile being 38 g and the frequency 1.9 times per week. Since 97% of the consumption of cruciferous vegetables came from white cabbage and cauliflower, our population is probably quite different from the others which also consume green cruciferous vegetables.

We did not find any association between meat intake and risk of colorectal cancer. Of the eight cohort studies reported thus far, some but not all have found a positive association. Two large US studies have found that high consumption of red meat increased risk [27, 29], whereas three other US cohorts found no association [23, 28, 43]. Meat intake was not associated with risk of colorectal cancer among the Seventh-day Adventists, either [44]. High consumption of processed meat increased the risk in a Dutch cohort [30] and in two of the four US cohorts [27, 28]. The only other Finnish cohort study found no association between consumption of either total meat or fried meat [45]. Our study population had a very high meat consumption level compared to the other cohorts. Also the range of total red meat intake from 79 to 203 g is wide and if meat as such would increase the risk of colorectal cancer one would assume to find the association in our population. For instance in the Health Professionals' Follow-up Study, the red meat consumption varied from 19 to 130 g [29]. However, not even high frequency of eating fried meat (about four times per week) increased the risk, which suggests that meat may not be harmful unless it has been fried or grilled heavily to get a brown surface [46, 47]. Our fried meat variable included all meat dishes which are normally prepared by frying the meat first. However, many of these foods are prepared with cooking in liquid after frying, which means that the frying time is shorter than in steaks which are quite seldom eaten in this population. We assume that the intake of heterocyclic amines from heavily-cooked meats is probably low due to the cooking methods, even though meat consumption as such is high. The consumption of processed meat, mostly sausages, was also higher than in the other cohorts, from 26 g/day in the lowest quartile to 122 g/day in the highest. This is reflected in a high level of nitrite intake, which was not, however, associated with risk of colorectal cancer. These data do not give support to the nitrosamine theory since the level of nitrosamines would provide enough substrate for their formation. In comparison, the consumption of processed meat was 0 g in the lowest and over 20 g in the highest quintile in the Dutch cohort study where consumption over 10 g increased risk of colorectal cancer [30]. The ratio of red meat over chicken and fish was also exceptionally high in our study, from 1.3 to 7.4, while in the Nurses' Health Study it varied from under 1.2 to over 5.1 and the risk seemed to increase from about 1.3 [27]. All these differences should be borne in mind when comparing and interpreting the results from different studies.

In conclusion, in contrast to the current hypotheses, intakes of fiber, fat or meat were not associated with risk of colorectal cancer. High calcium intake seemed to decrease the risk substantially. Since high meat intake did not increase risk of colorectal cancer in our population, where most of the meat is cooked in low temperatures and eaten as mixed dishes, recommendations concerning safe meat intake should focus on cooking methods rather than general meat restriction. Even though consumption of cruciferous vegetables seemed to increase risk of colorectal cancer, this finding

should be interpreted with caution. Since these analyses were conducted among smokers, the results may not be applicable to non-smoking populations.

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