

Dietary fat, cholesterol and colorectal cancer in a prospective study

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Summary The relationships between consumption of total fat, major dietary fatty acids, cholesterol, consumption of meat and eggs, and the incidence of colorectal cancers were studied in a cohort based on the Finnish Mobile Clinic Health Examination Survey. Baseline (1967–1972) information on habitual food consumption over the preceding year was collected from 9959 men and women free of diagnosed cancer. A total of 109 new colorectal cancer cases were ascertained late 1999. High cholesterol intake was associated with increased risk for colorectal cancers. The relative risk between the highest and lowest quartiles of dietary cholesterol was 3.26 (95% confidence interval 1.54–6.88) after adjusting for age, sex, body mass index, occupation, smoking, geographic region, energy intake and consumption of vegetables, fruits and cereals. Consumption of total fat and intake of saturated, monounsaturated, or polyunsaturated fatty acids were not significantly associated with colorectal cancer risk. Nonsignificant associations were found between consumption of meat and eggs and colorectal cancer risk. The results of the present study indicate that high cholesterol intake may increase colorectal cancer risk, but do not suggest the presence of significant effects of dietary fat intake on colorectal cancer incidence. © 2001 Cancer Research Campaign <http://www.bjcancer.com>

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Development of colorectal cancer has been suggested to be closely related to environmental exposures, especially those arising from diet. High dietary fat, protein (especially animal fat and protein), and consumption of meat have been frequently associated with increased incidence of large bowel cancers in ecological comparisons between and within countries (Armstrong and Doll, 1975; Rose et al, 1986). Results from animal studies also support the significance of fat intake in colon cancer development (Lipkin et al, 1999). Nevertheless, findings of epidemiologic studies on the relationship between fat consumption and colorectal cancer risk have been variable (Potter, 1996; Giovannucci and Goldin, 1997; Word Cancer Research Fund and American Institute for Cancer Research, 1997). High consumption of meat, especially red meat, was associated with elevated colorectal cancer risk in several case-control studies (Word Cancer Research Fund and American Institute for Cancer Research, 1997) and in some (Willett et al, 1990; Giovannucci et al, 1994; Singh and Fraser, 1998) but not in other prospective studies (Bostick et al, 1994; Goldbohm et al, 1994; Gaard et al, 1996; Kato et al, 1997; Pietinen et al, 1999).

Diets containing high amounts of animal fat also provide high amounts of cholesterol. It has been suggested that high cholesterol intake may be a risk factor for colorectal cancers (Cruse et al, 1979; Steinmetz and Potter, 1994). A recent combined analysis of case-control studies found significantly elevated risk for colorectal cancers associated with high cholesterol intake (Howe et al, 1997). Previous prospective studies have reported nonsignificant associations between dietary cholesterol and colorectal

cancer occurrence (Willett et al, 1990; Bostick et al, 1994; Giovannucci et al, 1994; Kato et al, 1997; Pietinen et al, 1999). In the present study we investigated the relationships between consumption of dietary fat, cholesterol, protein, meat and eggs and the incidence of colorectal cancer in a cohort based on the Finnish Mobile Clinic Health Examination Survey.

POPULATION AND METHODS

The subjects of this study were men and women who participated in a population-based health examination survey carried out in Finland during 1966–1972. A mailed invitation was sent to 33 382 men and 29 058 women who were selected to represent 30 populations from 6 regions of the country, and 81.9% of men and 83.2% of women participated in the examination. Approximately 1 in 5 of the participants were also interviewed for their total habitual diet at baseline started in 1967. Dietary data were collected for 9959 participants who were without diagnosed cancer at baseline. Identification of incident cancer cases during the follow-up until late 1999 was ascertained through the national Finnish Cancer Registry (Teppo et al, 1994). A total of 109 new colorectal cancer cases (63 in colon and 46 in rectum) were recognized as far as late 1999 (International Classification of Diseases, seventh revision, codes 153–154) (World Health Organization, 1955). The total number of men ($n = 54$) and women ($n = 55$) who developed colorectal cancer was approximately similar but the number of men with rectal cancer ($n = 25$) was slightly higher and the number with colon cancer ($n = 29$) lower than those of women.

Examinees who participated in the diet study were interviewed for their habitual food consumption during the preceding year. A structured questionnaire listing more than 100 different foods and mixed dishes was used to guide the interview carried out by interviewers who were trained home economic teachers and students in

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nutrition. Several of the questions were open-ended, requiring that they be specified by the respondent during the interview. Consumption of foods could be expressed per day, week, month, or year according to the choice of the respondent. Furthermore, foods whose consumption varied greatly between seasons could be estimated separately for different seasons. Food models made of plastic and rubber as well as samples of real food were available to aid in estimation of the amounts of foods consumed.

The average daily consumption of different food items and nutrients over all food items was computed utilizing a software package specifically developed for this study. The program utilized a recipe file that was compiled from recipes of mixed dishes available at the time of the baseline study. A food composition database to estimate the intake of nutrients over all food items was constructed based on Finnish food composition tables (Rastas et al, 1989). The fatty acid composition data were completed using analysed values in Finnish foods. More specific description of the dietary survey method and reproducibility of food and nutrient consumption at short-term and long-term interval were given in a previous study (Järvinen et al, 1993). Intraclass correlation coefficients for the intake of total protein, total fat, different major dietary fats and cholesterol varied from 0.65 to 0.80 over an interval of 4–8 months, and from 0.46 to 0.58 over an interval of 4–7 years. Long-term agreement for polyunsaturated fat intake was 0.26.

A self-administered questionnaire mailed with the invitation and checked during the examination provided information on sociodemographic factors, smoking, medical history, and use of drugs and food supplements. Weight and height in light indoor clothing without shoes were measured during the examination, and body mass index (kg m^{-2}) was calculated.

The associations between dietary variables and the incidence of colon and rectal cancers were investigated by utilizing the Cox proportional hazards model (Cox, 1972). The relative risks (RR) and 95% confidence intervals (CI) were calculated for different quartiles of food and nutrient intakes, using the lowest quartile as the reference category. Quartile ranges were determined separately for men and women. Age, sex, body mass index, occupation, smoking and geographic region were the nondietary covariates included in the model. Dietary energy intake and consumption of food groups of vegetables (without potatoes), fruits and cereals were added to the model as potential dietary confounders. Age, body mass index, energy intake and consumption of vegetables, fruits and cereals were added as continuous variables in the multivariate model whereas occupation (agricultural, industrial, services, white collar, housewives), smoking (never smoker, ex-smoker, current smoker of pipe or cigar, current smoker of fewer than 15 cigarettes per day, current smoker of 15 or more cigarettes per day) and geographical area (6 regions) were added as categorical variables. Age- and sex-adjusted mean intakes of foods and nutrients were estimated based on the general linear model.

RESULTS

At baseline colorectal cancer cases were older and their body mass index was significantly higher than that of the noncases (Table 1). The mean intake of dietary energy, protein and different fatty acids was approximately similar among colorectal cancer cases and noncases, but the cases consumed more eggs and cholesterol than the noncases, however, the differences were not statistically significant.

A slight nonsignificant decreased risk for colorectal cancers was suggested at the highest energy intake level (not shown in table).

Table 1 Selected baseline characteristics and mean daily intake of energy, nutrients and foods among the colorectal cancer cases and noncases

Variable ^a	Colorectal cancer cases (n = 109)	Noncases (n = 9850)	P value
Age, years ^b	49.5	39.0	<0.001
Body mass index, kg/m^2	25.6	24.8	0.02
Current smoking, %	31.8	35.3	0.42
Dietary energy, kcal	2516	2595	0.32
Protein, g	93.9	93.8	0.97
Total fat, g	109.1	109.1	0.99
Saturated fatty acids, g	61.6	61.6	0.99
Monounsaturated fatty acids, g	35.3	35.2	0.94
Polyunsaturated fatty acids, g	7.6	7.7	0.79
Cholesterol, mg	506	488	0.34
Meat and meat products, g	153.9	145.3	0.34
Eggs, g	36.2	34.1	0.47

^aAdjusted for age and sex. ^bAdjusted for sex.

The relative risk adjusted for age, sex, body mass index, occupation, smoking and geographical area was 0.78 (95% confidence interval (CI) 0.42–1.44) for colorectal cancers, 0.74 (95% CI = 0.32–1.71) for colon cancer, and 0.82 (95% CI = 0.33–2.04) for rectal cancer. In multivariate analysis including nondietary factors and potential dietary confounders the intakes of protein, total fat, and different major fatty acids were not significantly associated with colorectal cancer risk (Table 2), nevertheless, higher intake levels of total protein and monounsaturated fat were associated with a suggested increased risk of colorectal cancers.

High cholesterol intake predicted an elevated risk for colorectal cancers (Table 2). In multivariate analysis the relative risk for colorectal cancers was 3.26 (95% CI = 1.54–6.88) between the highest and lowest quartiles of dietary cholesterol. Significantly elevated risks were found for both colon (RR = 3.20, 95% CI = 1.21–8.48) and rectal (RR = 3.36, 95% CI = 1.05–10.80) cancers. The relative risk for colorectal cancers adjusted for non-dietary factors was 1.60 (95% CI = 0.92–2.79) and accordingly the higher relative risk in the final model was due to adjustment for energy intake. The relationship between dietary cholesterol intake and colorectal cancer risk persisted after further adjustment for total fat intake. The relative risk between the highest and lowest quartiles of cholesterol intake was 2.98 (95% CI = 1.39–6.39) in multivariate analysis including total fat intake (not shown in table).

Total consumption of meat and meat products, red meat, or liver was not significantly associated with the incidence of colorectal cancers (Table 3). Those who consumed poultry meat had an increased risk for colorectal cancers mainly due to an increased risk for colon cancer. Egg consumption was not significantly related to colorectal cancer risk. Nonsignificant associations were similarly found when we separately investigated eggs prepared by different cooking methods (not shown in table). The relative risk for colorectal cancers in the highest vs. lowest quartiles of fried egg consumption was 1.45 (95% CI = 0.82–2.55); the respective relative risk for consumption of boiled eggs was 1.01 (0.60–1.70).

DISCUSSION

In this prospective study, high cholesterol intake was found to be associated with increased risk of colorectal cancer. The demonstrated increased risk of colorectal cancer was likely to be specific for

Table 2 Relative risks (and 95% confidence intervals) for colorectal cancers in quartiles of intakes of dietary energy, protein, total fat, major fatty acids, and cholesterol

Quartile of daily intake	Quartile ranges		Colorectal cancer (n = 109) RR (95% CI) ^a	Colon cancer (n = 63) RR (95% CI) ^a	Rectum cancer (n = 46) RR (95% CI) ^a
	Men	Women			
Protein (g)					
1	<84.7	<59.2	1	1	1
2	84.7–103.2	59.2–72.9	2.26 (1.25–4.09)	1.80 (0.82–3.92)	3.13 (1.25–7.82)
3	103.3–126.5	73.0–89.6	2.19 (1.08–4.45)	2.06 (0.83–5.09)	2.37 (0.75–7.43)
4	>126.5	>89.6	2.28 (0.86–6.02)	1.59 (0.44–5.72)	3.69 (0.82–16.51)
Total fat (g)					
1	<95.7	<64.7	1	1	1
2	95.7–121.0	64.7–83.0	1.47 (0.82–2.66)	1.51 (0.68–3.33)	1.44 (0.60–3.49)
3	121.1–151.5	83.1–105.5	1.63 (0.80–3.33)	1.88 (0.73–4.85)	1.38 (0.47–4.08)
4	>151.5	>105.5	1.47 (0.52–4.20)	1.86 (0.46–7.43)	1.09 (0.22–5.41)
Saturated fatty acids (g)					
1	<53.5	<35.6	1	1	1
2	53.5–68.7	35.6–46.6	1.09 (0.60–1.99)	0.92 (0.41–2.07)	1.37 (0.56–3.36)
3	68.8–86.6	46.7–60.1	1.72 (0.88–3.36)	1.77 (0.74–4.25)	1.68 (0.59–4.80)
4	>86.6	>60.1	1.47 (0.56–3.83)	1.56 (0.44–5.48)	1.39 (0.31–6.14)
Monounsaturated fatty acids (g)					
1	<30.5	<20.8	1	1	1
2	30.5–38.8	20.8–26.7	1.52 (0.83–2.77)	1.44 (0.64–3.25)	1.63 (0.66–4.02)
3	38.9–49.2	26.8–34.0	2.10 (1.04–4.26)	2.40 (0.95–6.08)	1.74 (0.58–5.21)
4	>49.2	>34.0	2.37 (0.86–6.51)	2.37 (0.61–9.19)	2.38 (0.52–10.85)
Polyunsaturated fatty acids (g)					
1	<5.9	<4.1	1	1	1
2	5.9–7.7	4.1–5.5	0.98 (0.57–1.70)	0.84 (0.40–1.78)	1.20 (0.54–2.69)
3	7.8–10.3	5.6–7.5	1.12 (0.61–2.04)	1.31 (0.61–2.82)	0.84 (0.31–2.26)
4	>10.3	>7.5	1.13 (0.56–2.26)	0.97 (0.38–2.46)	1.35 (0.47–3.89)
Cholesterol (mg)					
1	<401.6	<288.3	1	1	1
2	401.6–517.2	288.3–380.3	1.79 (1.00–3.19)	1.64 (0.77–3.49)	2.05 (0.83–5.09)
3	517.3–668.0	380.4–501.0	2.04 (1.07–3.89)	1.84 (0.79–4.32)	2.36 (0.87–6.38)
4	>668.0	>501.0	3.26 (1.54–6.88)	3.20 (1.21–8.48)	3.36 (1.05–10.80)

^aRelative risk adjusted for age, sex, body mass index, occupation, smoking, geographical area, energy intake and consumption of vegetables, fruits and cereals.

Table 3 Relative risks (and 95% confidence intervals) for colorectal cancers in quartiles of intakes of meat and eggs

Quartile of daily intake (g)	Quartile ranges		Colorectal cancer (n = 109) RR (95% CI) ^a	Colon cancer (n = 63) RR (95% CI) ^a	Rectum cancer (n = 46) RR (95% CI) ^a
	Men	Women			
Meat, all					
1	<101	<67	1	1	1
2	101–151	67–101	1.07 (0.62–1.86)	0.75 (0.36–1.58)	1.71 (0.74–3.97)
3	152–220	102–145	1.31 (0.73–2.32)	1.06 (0.49–2.26)	1.77 (0.72–4.35)
4	>220	>145	1.52 (0.78–2.96)	1.54 (0.66–3.57)	1.48 (0.49–4.45)
Red meat					
1	<94	<61	1	1	1
2	94–141	61–92	1.06 (0.67–2.01)	0.71 (0.33–1.51)	2.18 (0.93–5.10)
3	142–206	93–134	1.55 (0.88–2.73)	1.29 (0.63–2.66)	2.11 (0.84–5.28)
4	>206	>134	1.50 (0.77–2.94)	1.34 (0.57–3.15)	1.82 (0.60–5.52)
Poultry					
1 (no)			1	1	1
2 (yes)			1.59 (1.04–2.44)	1.93 (1.12–3.35)	1.20 (0.60–2.37)
Liver					
1	<1	<1	1	1	1
2	1	1–2	0.84 (0.46–1.51)	0.79 (0.37–1.69)	0.92 (0.37–2.30)
3	2–5	3–5	0.94 (0.55–1.58)	0.96 (0.49–1.88)	0.90 (0.39–2.08)
4	>5	>5	1.03 (0.60–1.77)	0.87 (0.42–1.80)	1.26 (0.57–2.81)
Eggs					
1	<17	<13	1	1	1
2	17–29	13–24	0.84 (0.49–1.45)	0.72 (0.35–1.47)	1.06 (0.45–2.47)
3	30–48	25–42	1.09 (0.65–1.84)	0.99 (0.50–1.93)	1.27 (0.56–2.90)
4	>48	>42	1.22 (0.70–2.13)	1.02 (0.48–2.14)	1.54 (0.66–3.64)

^aRelative risk adjusted for age, sex, body mass index, occupation, smoking, geographical area, energy intake, and consumption of vegetables, fruits and cereals.

dietary cholesterol since the association was independent of dietary fat intake, and important food sources of dietary cholesterol, meat and eggs, showed only nonsignificant relationships with colorectal cancer risk. However, we cannot exclude the possibility that the association suggested for dietary cholesterol was due to other dietary or life-style habits potentially related to cholesterol intake.

Results from animal studies indicate that cholesterol acts as a cocarcinogen in the development of colon cancer. Feeding animals with high-cholesterol diets increased the number of induced colon cancers (Cruse et al, 1978; Hiramatsu et al, 1992) and enhanced the induction and development of colonic preneoplastic lesions in carcinogen-treated animals (Rao et al, 1992). There are several mechanisms by which cholesterol intake could modify the carcinogenic process (Steinmetz and Potter, 1994). However, the effect of cholesterol may be dependent on whether it is given during early or later stages of cancer development. When fed to animals only during the promotion stage, cholesterol may even decrease the appearance of induced colon tumours (Cohen et al, 1982; El-Sohemy et al, 1996).

Findings from previous epidemiological studies on the relationship between dietary cholesterol and colorectal cancer risk have been variable. An ecological study between countries illustrated a close correlation between intake of cholesterol and colon cancer mortality after adjustment for intake of fat and dietary fibre (Liu et al, 1979). A combined analysis of 13 case-control studies from different countries demonstrated a significant direct relationship between dietary cholesterol intake and the occurrence of colorectal cancers (Howe et al, 1997). The findings of previous prospective studies suggested null associations; reported relative risks for colon/colorectal cancers between the highest and lowest cholesterol intake categories varied between 0.91–1.39 (Willett et al, 1990; Bostick et al, 1994; Giovannucci et al, 1994; Kato et al, 1997; Pietinen et al, 1999). The considerably longer follow-up period in the present study (up to 32 years) than in previous studies, in addition to other differences in the study populations, may offer some explanations for the differences in the findings. It may be possible that the period of exposure to dietary cholesterol is important in relation to colorectal cancer development. Due to a long follow-up period we may have been able to detect risk factors that operate at earlier stages of carcinogenesis. It has been suggested that the absolute amounts of cholesterol consumed as a factor in itself might not be as significant as its relationship to the intake of total plant sterols (Nair et al, 1984). Plant sterols may offer protection from cancers by different mechanisms (Awad and Fink, 2000). In the present study population cholesterol intake was relatively high, whereas the intake of phytosterols was apparently low due to especially low consumption of vegetable fats.

Eggs have high contents of cholesterol and can contribute importantly to total cholesterol intake. In epidemiologic studies, findings on the relationship between egg consumption and colorectal cancer have been mixed. Approximately half of the 16 recently reviewed case-control studies reported elevation in the risk of large bowel cancers associated with egg consumption (World Cancer Research Fund and American Institute for Cancer Research, 1997). Results of a recent large case-control study also addressed the importance of egg consumption in relation to colorectal cancer risk (Le Marchand et al, 1997). One previous prospective study among a low-risk population presented a positive association between egg consumption and the risk of fatal colon cancer during a fairly long follow-up period (Phillips and

Snowdon, 1985). In the present study egg consumption was not significantly associated with colorectal cancer risk.

We found no significant associations between the intake of total fat or different major fatty acids and risk of colorectal cancers. These results are in line with the finding from several previous prospective studies (Bostick et al, 1994; Giovannucci et al, 1994; Goldbohm et al, 1994; Gaard et al, 1996; Kato et al, 1997; Pietinen et al, 1999). A combined analysis of 13 case-control studies controlling for total dietary energy intake and dietary cholesterol revealed no significant associations between intake of total fat or any of the major fatty acids and colorectal cancer risk (Howe et al, 1997). However, an elevated colon cancer risk was associated with intake of total fat and animal fat as well as with consumption of saturated and monounsaturated fats in a prospective study of female nurses in the USA (Willett et al, 1990).

Total consumption of protein and meat was not significantly associated with colorectal cancer risk in the present study. Previous prospective studies have also reported nonsignificant associations (Willett et al, 1990; Bostick et al, 1994; Giovannucci et al, 1994; Goldbohm et al, 1994; Pietinen et al, 1999), or decreased risk for colorectal cancers with higher protein intakes (Kato et al, 1997), whereas associations of different protein sources with colon cancer risk have been more variable. Red meat consumption in particular was associated with increased colon cancer risk in large prospective studies from the United States (Willett et al, 1990; Giovannucci et al, 1994) but not consistently in other prospective studies (Bostick et al, 1994; Goldbohm et al, 1994; Kato et al, 1997; Pietinen et al, 1999). In addition to fatty acid composition of meat, heterocyclic amines formed during frying and broiling of meat, nitrosamines present in processed meat products or formed in the intestinal contents, and iron provided by meat have been suggested as potential factors which may explain increased colorectal cancer risk with high red meat consumption (Giovannucci and Goldin, 1997). In the present study, the total consumption of meat and red meat showed nonsignificant relationships with colorectal cancer incidence during the follow-up. In our previous studies no significant relationships between consumption of fried meat and colorectal cancer were observed (Knekt et al, 1994), whereas higher consumption of cured meat besides salted and smoked fish, all representing important sources of nitrosamines in the diet, were associated with higher colorectal cancer risk (Knekt et al, 1999).

Prospective study design and comprehensive dietary survey method were obvious advantages in the present study. Due to comprehensive dietary interview method we were able to allow for dietary energy intake which is suggested to be an important confounder in colorectal cancer studies (Giovannucci and Goldin, 1997; Slattery et al, 1997). On the other hand, due to the relatively small number of cancer cases the power of the study to reveal associations could have been diminished. During the long follow-up period dietary habits of participants may have changed. Nevertheless, the results from dietary measurements repeated several years apart suggested moderate agreement on the intake of nutrients under consideration with an exception of polyunsaturated fatty acids (Järvinen et al, 1993).

The findings in this prospective study suggest that high cholesterol intake may be a risk factor for colorectal cancers, whereas no significant relationships were observed between colorectal cancer

incidence and the intake of total fat, various major fatty acids, or total dietary protein.

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