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Vegetable and animal products as determinants of colon cancer risk in Dutch men and women

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To examine the relationship between colon cancer and food groups from vegetable or animal sources and their possible interactions with gender, we analyzed data from a Dutch case-control study. Dietary patterns were assessed for 232 colon cancer cases and 259 population controls. In multivariate analyses, the consumption of vegetables was associated significantly with reduced colon-cancer risk (odds ratio [OR] for highest *cf* lowest quartile of consumption = 0.4, 95 percent confidence interval [CI] = 0.2-0.7, *P*-trend = 0.0004). Consumption of fresh red meat was associated positively with risk in women (OR = 2.4, 95% CI = 1.0-5.7, *P*-trend = 0.04), especially for those with a high consumption of red meat relative to the consumption of vegetables and fruits (OR = 3.1). For men, no association with consumption of fresh red meat was found (OR = 0.9). No clear associations were found for other products of vegetable or animal origin. The results of this Dutch case-control study support the preventive potential of a high-vegetable diet in colon cancer risk. This study suggests this may be important for women consuming a diet high in red meat. *Cancer Causes and Control* 1995, 6, 225-234

Key words: Animal products, colon cancer, gender interactions, Netherlands, vegetable products.

Introduction

Colon cancer is one of the most prominent types of cancer in the Netherlands, as in many other Westernized countries. In Dutch men, about 30 new cases of colon cancer are diagnosed per annum per 100,000 population. For Dutch women, the incidence is about 35 per 100,000.[1]

Dietary patterns are considered to contribute importantly to the etiology of colon cancer. Research has focused primarily on two nutrient hypotheses: dietary fiber is protective, while fat intake increases the risk of colon cancer.[2] Results have been both affirmative and contradictory for nutrients and food groups.[2]

Currently, the dietary fiber hypothesis is interpreted as an effect primarily of vegetables and/or fruits, with a variety of nutrients and bioactive substances relevant to the prevention of cancer of the colon as well as many other cancer sites.[3] Although several epidemiologic studies have addressed the association between colon cancer risk and the consumption of vegetables and fruits as reviewed by Steinmetz and Potter[3] and Block *et al*,[4] none of these studies was conducted in the Netherlands. About two-thirds of the case-control studies[5-19] conducted in Westernized countries observed an inverse association with colon cancer risk for at least one vegetable and/or fruit food group,[5-19] while others[20-24] reported no association or a positive one.

Consumption of red meat is one of the major sources of saturated fat in a Westernized diet. In contrast to the

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consumption of vegetables, red meat consumption in relation to colon cancer risk has been studied in the Netherlands Cohort Study on diet and cancer[25] which showed no important association between red meat consumption and colon cancer risk. Although supported by other studies,[6,17,18,22,26] these findings contradict results of several studies[5,12,14,16,19,24,27,28] showing a significant positive association with red meat consumption. Although differences in dietary methodology and subject recruitment might partially account for such inconsistencies, the population level and variability in the consumption of vegetables and fruits plausibly modifies the effects of meat consumption. Substances in red meat, which promote or initiate carcinogenic processes, might be inhibited by protective substances in vegetables and fruits, which, according to Steinmetz and Potter,[29] makes it biologically meaningful to study the ratio between these two food groups. In their study, this ratio was higher, although not significantly so, for colon cancer cases than for controls both in men and women.[29] It is especially interesting to study this ratio of red meat to vegetables and fruits in a Dutch population. The Dutch, traditionally, have one hot meal a day, which includes fresh meat (beef, pork, minced meat, chicken, or fish, usually pan-fried or stewed) together with vegetables and (usually) potatoes. At the population level, the variability in the consumption of vegetables and meat is high.

Another intriguing aspect of colon cancer is the suggested gender difference in etiology. There are many indications that the association between diet and colon cancer might differ between men and women.[2] However, previous studies reporting gender-stratified analyses[7,10,13,19,29] have produced inconsistent findings.

In a case-control study, we examined the role of vegetables, fruits, red meat, and their ratio in relation to colon cancer in Dutch men and women. In addition, we explored associations and potential gender interactions for other food groups of vegetable and animal origin—such as potatoes,[30] dairy products,[31] eggs,[29] fish and poultry[27]—that have been linked to the risk of colon cancer. Since interpretation in terms of preventive potentials is easier, we focused primarily on the consumption of food groups.

Materials and methods

Subjects

The population-based case-control study was conducted in the Netherlands between 1989 and 1993. Cases were defined as male and female patients with newly diagnosed adenocarcinoma of the colon (ICD-O[32] code 153). They were recruited from regional hospitals from eastern and central regions of the Netherlands. The cancer registries of these areas were used as a check on completeness and provided additional clinical and pathological information. Cases were western Europeans with Dutch nationality who, at the time of diagnosis, were up to 75 years old and did not have previous cancer, polyposis coli, ulcerative colitis, or Crohn's disease. For 28 cases, the cancer registry defined the location of the tumor as rectosigmoid in contrast with the surgeon who localized the tumor in the colon. Analyses were conducted including, as well as excluding, these cases.

Of all eligible cases diagnosed in the cooperating hospitals, 47 percent were invited to participate. Exclusion was due mainly to organizational limitations within the hospitals. Comparison with the cancer registry data showed that exclusion occurred nonsystematically: cases invited did not differ importantly from those not invited in age, gender, urbanization level, and site distribution. However, cases who were not invited did have a worse prognosis according to Duke's status[33] and more frequently had undergone radiotherapy and chemotherapy. Of those invited, 60 percent (64 percent of the men, 57 percent of the women) agreed to be interviewed. Of the total eligible cases, 57 percent had Duke's A and B (lower stage) tumors, compared with 64 percent of the participating cases. Except for Duke's classification status, the distributions of age, gender, tumor site, and therapies of the interviewed cases were comparable to the distributions among all eligible cases. In order to explore potential selection bias, participants and nonparticipants were asked to fill out a short questionnaire on lifestyle habits and the frequency of consumption of dairy products, bread, and meat. All participating cases and 23 percent of the nonparticipating cases filled out the questionnaire and returned it. Cases participating in the interview did not differ significantly in consumption of food groups of major interest from those nonparticipants who filled out the short questionnaire.

The population controls were recruited randomly by general practitioners of participating cases, using the same eligibility criteria as for the cases. They were frequency-matched to the cases on age, gender, and degree of urbanization. For each case, the general practitioner received a standardized form with three-letter strings, randomly obtained from the local telephone directory, to initiate the search for controls in his or her own database. For each string, the first subject who matched the eligibility criteria was sent a standard letter of invitation signed by his/her general practitioner, including a reply form to the investigator. Of the 520 controls invited, 57 percent agreed to participate in the interview (55 percent of the men, 59 percent of the women). Participation was higher among

younger people and those living in urban areas. Meat consumption and other dietary and lifestyle patterns did not differ importantly between those who participated in the interview and those who refused to participate but completed the nonresponse questionnaire (42 percent of the nonparticipants).

Data collection

Cases and controls were interviewed on dietary habits and lifestyle factors in their own homes by qualified dietitians. For cases, the interval between diagnosis and interview was three to six months. Each dietitian interviewed a similar number of cases and controls in a geographic area. The dietary part of the questionnaire requested information on frequency of consumption in the year before the interview (for cases, before diagnosis or complaints) and consisted of a detailed, structured, dietary history questionnaire, covering the complete dietary pattern. Questions included frequency of consumption per month, number of months in which the item was consumed, number of portions per consumption, and size of the portions of 289 food items from 19 food groups. To be able to estimate portion sizes, frequently-used household utensils and cups were filled with water and weighed after the interview.

To minimize errors, the dietary history questionnaire was entered into the computer using a specially designed computer program which included range-checks and cross-checks. The internal consistency of frequency of consumption of various meal components was checked with the total meal pattern. Consumption frequencies of individual items, as well as the frequency of consumption of the total food group, were ascertained. Whenever the total frequencies of the specific items did not match the frequency of the total food group, a correction factor was calculated automatically and used to adjust the consumption frequency of the individual food items. Average daily intake of nutrients was calculated using the Dutch Food Composition Table.[34] Intake of nutrients was adjusted for energy intake by regression analysis for men and women separately.[35]

In addition to diet, subjects were asked about sociodemographic characteristics (*e.g.*, age, urbanization level, education, and occupation), menstrual and reproductive history for women, positive family history of colon cancer, personal medical history, smoking habits, and past use of medications. To address stability of food habits, questions included changes in habits as a result of gastrointestinal complaints.

Data analysis

Differences in demographic, predisposing, dietary and lifestyle factors were compared between cases and controls. The individual food items in the questionnaire were categorized into major food groups (*e.g.*, vegetables, fruit, red meat [including fresh red meat], and poultry) whose intake was expressed in grams per day. Ratios were calculated for red meat to vegetables and fruits, and for red meat to poultry and fish. In calculating ratios, nonusers were excluded from the analyses (four nonusers of red meat and 26 nonusers of fish or poultry; each participant consumed vegetables or fruits). Inclusion of nonusers did not change the results importantly (data not shown).

Nutrient intake, food group consumption and the ratios were divided into quartiles according to the distribution in the control group. Odds ratios (OR) for colon cancer as estimates of relative risks, together with their approximate 95 percent confidence intervals (CI),

Table 1. Mean and standard deviation (SD) of some characteristics in colon cancer cases and controls, the Netherlands

Characteristics	Cases ($n = 232$) Mean ± SD	Controls ($n = 259$) Mean ± SD
Demographic factors		
Age (yrs)	62 ± 10	62 ± 10
Gender (% male)[a]	56 ± 3	53 ± 3
Urbanization level (% urban)[a]	48 ± 3	53 ± 5
Socioeconomic status (% blue collar)[a]	46 ± 9	40 ± 3
Predisposing factors		
Family history of colon cancer (%)[a]	18 ± 3	11 ± 2
Cholecystectomy (%)[a]	10 ± 7	5 ± 6
Dietary factors[b]		
Total energy intake (kJ)	10,433 ± 3,234	9,362 ± 2,844[a]
Total fat (g)	104 ± 25	101 ± 25
Total carbohydrates (g)	246 ± 58	254 ± 52
Total protein (g)	85 ± 17	84 ± 15
Dietary fiber (g)	28 ± 9	29 ± 8
Vitamin C (mg)	105 ± 53	118 ± 54[c]
Lifestyle factors		
Body mass index (kg/m^2)	26 ± 4	26 ± 4
Current smokers (%)[a]	29 ± 3	33 ± 3
Alcohol (g)[b]	11 ± 25	14 ± 18
Supplement use		
Total (%)[a]	34 ± 3	37 ± 3
Calcium and or vitamin D (%)[a]	11 ± 2	19 ± 2[c]

[a] Standard error = (p(1-p)/n).
[b] Adjusted for total energy intake by regression analysis, for men and women separately.
[c] $P < 0.05$.

Table 2a. Vegetable and animal products and risk of colon cancer (both genders combined) per quartile (Q), odds ratios (OR) and 95% confidence intervals (CI), the Netherlands

Variable	Q1 (lowest)	Q2	Q3	Q4 (highest)	χ^2trend (*P*-value)	χ^2gender interactions (*P*-value)
Vegetable products						
Vegetables (g/day)	< 142	142-191	192-247	> 247		
Cases/controls	81/65	68/65	48/65	35/64		
OR (CI)[a]	1.00	0.82 (0.50-1.32)	0.57 (0.34-0.95)	0.40 (0.23-0.69)		1.52 (0.22)
OR (CI)[a]	1.00	0.73 (0.45-1.21)	0.53 (0.32-0.89)	0.40 (0.23-0.69)	12.58 (0.0004)	
Fruits (g/day)	< 125	125-198	199-288	> 288		
Cases/controls	62/65	63/65	51/65	56/64		
OR (CI)[a]	1.00	0.95 (0.57-1.58)	0.78 (0.46-1.32)	0.76 (0.45-1.29)		4.12 (0.04)
OR (CI)[b]	1.00	0.97 (0.58-1.53)	0.79 (0.46-1.63)	0.82 (0.84-1.41)	0.80 (0.37)	
Potatoes (g/day)	< 79	79-115	116-171	> 171		
Cases/controls	55/67	62/64	69/65	46/63		
OR(CI)[a]	1.00	1.23 (0.74-2.07)	1.16 (0.69-1.95)	0.62 (0.34-1.12)		0.13 (0.72)
OR(CI)[b]	1.00	1.23 (0.73-2.08)	1.24 (0.73-2.11)	0.67 (0.37-1.22)	1.77 (0.18)	
Cereal products (g/day)	< 121	121-159	160-200	> 200		
Cases/controls	56/66	55/64	45/68	76/61		
OR (CI)[a]	1.00	0.96 (0.57-1.62)	0.60 (0.35-1.05)	0.99 (0.55-1.77)		0.62 (0.43)
OR (CI)[b]	1.00	1.08 (0.63-1.85)	0.69 (0.39-1.21)	1.16 (0.63-2.14)	0.08 (0.77)	
Animal products						
Red meat (g/day)	< 52	52-72	73-94	> 94		
Cases/controls	55/67	46/64	59/67	72/61		
OR (CI)[a]	1.00	0.84 (0.49-1.43)	0.97 (0.58-1.63)	1.18 (0.70-2.00)		5.45 (0.02)
OR (CI)[a]	1.00	0.80 (0.47-1.38)	0.91 (0.54-1.55)	1.11 (0.65-1.90)	0.30 (0.58)	
Poultry (g/day)	< 5	5-10	11-21	> 21		
Cases/controls	67/77	53/53	66/71	46/58		
OR (CI)[a]	1.00	1.08 (0.65-1.82)	1.08 (0.67-1.74)	0.86 (0.51-1.45)		0.70 (0.40)
OR (CI)[b]	1.00	1.00 (0.59-1.70)	1.04 (0.64-1.70)	0.79 (0.46-1.35)	0.71 (0.40)	
Fish (g/day)	< 5	5-12	13-24	> 24		
Cases/controls	64/70	41/62	49/63	78/64		
OR (CI)[a]	1.00	0.72 (0.42-1.22)	0.85 (0.51-1.43)	1.15 (0.70-1.89)		0.36 (0.55)
OR (CI)[b]	1.00	0.73 (0.42-1.24)	0.85 (0.50-1.44)	1.13 (0.68-1.87)	0.84 (0.36)	
Dairy products (g/day)	< 270	270-404	405-588	> 588		
Cases/controls	55/65	51/66	44/64	82/64		
OR (CI)[a]	1.00	0.84 (0.49-1.42)	0.71 (0.41-1.21)	1.13 (0.67-1.89)		2.00 (0.16)
OR (CI)[b]	1.00	0.88 (0.52-1.51)	0.77 (0.44-1.34)	1.27 (0.75-2.17)	1.45 (0.23)	
Eggs (g/day)	< 8	8-12	13-19	> 19		
Cases/controls	49/65	46/66	69/69	68/59		
OR (CI)[a]	1.00	0.86 (0.50-1.48)	1.19 (0.71-2.00)	1.22 (0.71-2.08)		0.31 (0.58)
OR (CI)[b]	1.00	0.86 (0.50-1.49)	1.22 (0.72-2.06)	1.17 (0.68-2.01)	0.79 (0.38)	
Red meat/poultry + fish						
Ratio	< 1.33	1.33-2.52	2.52-4.73	> 4.73		
Cases/controls[c]	48/61	61/61	57/60	51/62		
OR (CI)[a]	1.00	1.14 (0.67-1.95)	1.18 (0.69-2.02)	1.07 (0.62-1.86)		1.88 (0.17)
OR (CI)[b]	1.00	1.05 (0.61-1.81)	1.22 (0.71-2.11)	1.05 (0.60-1.84)	0.01 (0.92)	

Continued...

Table 2a. Continued

Variable	Q1 (lowest)	Q2	Q3	Q4 (highest)	χ^2trend (*P*-value)	χ^2gender interactions (*P*-value)
Red meat/vegetables + fruits						
Ratio	< 0.11	0.11-0.18	0.18-0.27	> 0.27		
Cases/controls[c]	41/64	53/63	60/65	76/65		
OR (CI)[a]	1.00	1.33 (0.77-2.31)	1.47 (0.85-2.54)	1.82 (1.06-3.13)		16.23 (0.0001)
OR (CI)[b]	1.00	1.26 0.72-2.22)	1.45 (0.83-2.52)	1.76 (1.01-3.07)	4.00 (0.05)	

[a] Adjusted for age, gender, urbanization level, and total energy intake.
[b] Adjusted for age, gender, urbanization level, total energy intake, alcohol use, cholecystectomy, and family history of colon cancer.
[c] Nonusers of food groups included in the denominator and/or nominator were excluded from these analyses.

were calculated by maximum likelihood estimation using BMDP software,[36] taking the lowest quartile of exposure as the reference. To account simultaneously for the potential confounding effect of age, gender, urbanization level, energy intake, vitamin C intake (only with nutrient intake), family history of colon cancer, cholecystectomy, socioeconomic status, body mass index (BMI) (height/weight^2), smoking habits, and alcohol intake, multiple logistic regression models were used. Decisions on which covariates to include in the final models were based on: (i) evidence from epidemiologic literature; (ii) biological plausibility; (iii) whether the regression coefficient of the primary independent variable changed by 10 percent or more after addition of the potentially confounding variable; and/or (iv) whether the covariate entered the model at the 0.10 level of significance.

Chi-square tests for trend were conducted using the median of each quartile as a continuous variable. Chi-square tests for gender interaction were conducted. Additionally, ORs of those food groups for which an interaction with gender was observed were calculated for men and women separately, with the quartiles based on the distribution of the intake among male and female controls, respectively.

Results

Mean age was similar among cases and controls (Table 1). The case group included more men, fewer current smokers, fewer people living in urban areas, and a higher proportion of people with lower socioeconomic status.

Family history of colon cancer and cholecystectomy was more frequent among cases. The intake of energy, and energy-adjusted intake of total fat and total protein were higher among cases, while energy-adjusted intake was lower for total carbohydrates, dietary fiber, vitamin C, and alcohol. Total supplement use and use of specific calcium and vitamin D supplements tended to be lower in cases. Cases and controls did not differ in BMI.

Table 2a presents ORs of colon cancer for quartiles of intakes of several food groups. Considering food groups of vegetable origin, a significant inverse association with vegetable consumption was found after adjustment for total energy and for variables for which frequency matching occurred. For other food groups of vegetable origin, no significant associations were found, with ORs ranging from 0.67 for potatoes to 1.16 for cereal products (Table 2a). For the consumption of legumes, no important association was found (OR = 1.08, CI = 0.67-1.76). However, in this population, legumes were consumed too infrequently to draw firm conclusions.

Additional adjustment for other covariates (cholecystectomy, family history, and alcohol use) did not change the ORs appreciably. Socioeconomic status, any supplement use, BMI, smoking habits, and total fat intake did not enter the multivariate model at the 0.10 level of significance, did not alter the estimates appreciably, and therefore were not included in the models.

For intake of animal products, nonsignificant positive associations were found for red meat, dairy products, and eggs. A nonsignificant inverse association was found for poultry consumption. The consumption ratio of red meat to poultry and fish was not associated importantly with risk. The ratio of red meat to vegetables and fruits, however, was related positively to risk.

No gender interactions were observed, except for the consumption of fruits, red meat, and the ratio of red meat to vegetables and fruits.

Table 2b presents ORs for colon cancer by quartiles of total energy intake and by quartiles of energy-adjusted nutrients from vegetable and animal sources.

Table 2b. Total energy intake and the intake of energy-adjusted nutrients and risk of colon cancer (both genders combined) per quartile (Q), odds ratios (OR) and 95% confidence intervals (CI), the Netherlands

Variable	Q1 (lowest)	Q2	Q3	Q4 (highest)	χ^2trend (*P*-value)	χ^2gender interactions (*P*-value)
Energy intake (kJ)	< 7,476	7,476-8,857	8,858-11,097	> 11,097		
Cases/controls	39/65	46/65	57/65	90/64		
OR (CI)[a]	1.00	1.36 (0.76-2.41)	1.74 (0.98-3.08)	3.17 (1.70-5.91)		0.48 (0.49)
OR (CI)[b]	1.0	1.36 (0.76-2.45)	1.82 (1.01-3.30)	3.47 (1.83-6.58)	17.57 (0.0000)	
Vitamin C[c]	< 79.0	79.0-110.8	110.8-146.6	> 146.6		
Cases/controls	73/65	73/65	49/65	37/64		
OR (CI)[a]	1.00	1.04 (0.64-1.69)	0.66 (0.40-1.11)	0.51 (0.30-0.88)		2.53 (0.11)
OR (CI)[b]	1.00	1.07 (0.65-1.76)	0.70 (0.42-1.19)	0.53 (0.31-0.92)	6.91 (0.009)	
β-carotene[c]	< 1.8	1.8-2.4	2.4-3.4	> 3.4		
Cases/controls	81/63	50/67	53/65	48/64		
OR (CI)[a]	1.00	0.64 (0.39-1.07)	0.69 (0.42-1.15)	0.60 (0.36-1.00)		0.32 (0.57)
OR (CI)[b]	1.00	0.64 (0.38-1.06)	0.70 (0.42-1.16)	0.61 (0.36-1.03)	2.91 (0.09)	
Dietary fiber[c]	< 23.1	23.1-27.8	27.8-33.4	> 33.4		
Cases/controls	82/65	49/65	49/65	52/64		
OR (CI)[a]	1.00	0.58 (0.35-0.97)	0.58 (0.34-0.97)	0.56 (0.33-0.95)		3.54 (0.06)
OR (CI)[b]	1.00	0.57 (0.34-0.96)	0.63 (0.37-1.06)	0.62 (0.36-1.08)	2.47 (0.12)	
Animal protein[c]	< 48.2	48.2-56.5	56.5-65.4	> 65.4		
Cases/controls	54/65	45/65	66/65	67/64		
OR (CI)[a]	1.00	0.87 (0.50-1.50)	1.40 (0.82-2.40)	1.25 (0.72-2.17)		0.09 (0.77)
OR (CI)[b]	1.00	0.85 (0.48-1.49)	1.39 (0.80-2.41)	1.32 (0.75-2.33)	1.88 (0.17)	
Saturated fat	< 33.4	33.4-40.7	40.7-49.5	> 49.5		
Cases/controls	42/64	64/66	64/65	62/64		
OR (CI)[a]	1.00	1.71 (0.99-2.95)	1.80 (0.96-3.38)	1.63 (0.82-3.23)		0.44 (0.51)
OR (CI)[b]	1.00	1.53 (0.87-2.69)	1.55 (0.80-3.01)	1.37 (0.66-2.85)	0.08 (0.78)	
Cholesterol[c]	< 226.2	226.2-286.0	286.0-347.2	> 347.2		
Cases/controls	45/65	59/65	60/65	68/64		
OR (CI)[a]	1.00	1.58 (0.92-2.73)	1.71 (0.97-3.03)	1.73 (0.95-3.14)		0.53 (0.47)
OR (CI)[b]	1.00	1.43 (0.82-2.50)	1.54 (0.86-2.78)	1.48 (0.80-2.76)	1.21 (0.27)	

[a] Adjusted for age, gender, urbanization level and total energy intake.

[b] Adjusted for age, gender, urbanization level, total energy intake, alcohol intake, vitamin C use (not for β-carotene and dietary fiber), cholecystectomy, family history of colon cancer.

[c] mg per day, or g (for dietary fiber, animal protein, saturated fat), adjusted for total energy intake by regression, for men and women separately.

Energy intake was associated positively with colon cancer. For nutrients related to vegetable intake (dietary fiber, β-carotene, vitamin C), inverse associations with risk were found. As a consequence, inclusion of vitamin C in the multivariate model attenuated the ORs for dietary fiber and β-carotene (data not shown). Nutrients related to meat intake (saturated fat, animal protein, cholesterol) were found to be associated positively, but nonsignificantly, with risk.

For the food groups that showed an interaction with gender (Table 2a), gender-specific ORs are presented in Table 3. For women, but not men, a nonsignificant inverse association with consumption of fruits was found, and a significantly increasing trend was evident for red meat consumption. Adjustment for saturated fat intake did not appreciably modify these results; saturated fat intake therefore was not included in the model.

When participants (33 cases and 10 controls) who indicated that they had altered their dietary pattern as a result of gastrointestinal distress were excluded from the analyses, results did not change appreciably either (data not shown).

Table 3. Gender-specific associations of fruits, red meat, and the ratio of meat to vegetables and fruit with the risk of colon cancer

Variable	Q1 (lowest)	Q2	Q3	Q4 (highest)	χ^2trend (*P*-value)
Fruits					
Men					
g/day	< 100	100-162	162-269	> 269	
Cases/controls	36/34	25/34	30/34	39/34	
OR (CI)[a]	1.00	0.73 (0.36-1.49)	0.80 (0.40-1.61)	0.94 (0.48-1.86)	
OR (CI)[b]	1.00	0.77 (0.37-1.61)	0.84 (0.41-1.72)	1.00 (0.49-2.03)	0.02 (0.88)
Women					
g/day	< 143	143-241	242-327	> 327	
Cases/controls	31/31	30/31	24/31	17/30	
OR (CI)[a]	1.00	0.86 (0.41-1.80)	0.77 (0.36-1.69)	0.48 (0.21-1.09)	
OR (CI)[b]	1.00	0.89 (0.42-1.89)	0.82 (0.38-1.79)	0.54 (0.23-1.23)	2.27 (0.13)
Red meat					
Men					
g/day	< 60	60-83	84-102	> 102	
Cases/controls	33/34	35/36	24/33	38/33	
OR (CI)[a]	1.00	0.82 (0.41-1.65)	0.62 (0.30-1.30)	0.96 (0.47-1.92)	
OR (CI)[b]	1.00	0.80 (0.39-1.61)	0.57 (0.27-1.30)	0.89 (0.43-1.81)	0.25 (0.62)
Women					
g/day	< 38	38-59	60-83	> 83	
Cases/controls	12/31	25/33	36/31	29/28	
OR (CI)[a]	1.00	2.05 (0.86-4.88)	2.82 (1.21-6.56)	2.40 (1.01-5.73)	
OR (CI)[b]	1.00	1.82 (0.75-4.46)	2.71 (1.15-6.38)	2.35 (0.97-5.66)	4.09 (0.04)
Red meat/vegetables + fruits					
Men					
Ratio	< 0.14	0.14-0.22	0.22-0.33	> 0.33	
Cases/controls	32/34	33/32	24/35	40/34	
OR (CI)[a]	1.00	1.09 (0.54-2.20)	0.79 (0.38-1.61)	1.28 (0.64-2.56)	
OR (CI)[b]	1.00	1.04 (0.51-2.13)	0.79 (0.38-1.64)	1.18 (0.57-2.43)	0.16 (0.69)
Women					
Ratio	< 0.09	0.09-0.13	0.13-0.20	> 0.20	
Cases/controls	16/33	11/26	26/32	48/31	
OR (CI)[a]	1.00	0.92 (0.36-2.36)	1.65 (0.73-3.71)	3.04 (1.41-6.56)	
OR (CI)[b]	1.00	0.81 (0.30-2.17)	1.53 (0.67-3.51)	3.05 (1.39-6.71)	11.64 (0.0006)

[a] Adjusted for age, urbanization level and total energy intake.
[b] Adjusted for age, urbanization level, total energy intake, alcohol intake, family history of colon cancer, and cholecystectomy.

Discussion

Of those products of vegetable and animal origin studied, the consumption of vegetables was found to be associated inversely with colon cancer risk. In addition, for women, a nonsignificant inverse association was found for fruit consumption, while red meat consumption increased risk.

Methodologic considerations

In each retrospective case-control study, selection and information bias might affect the internal validity. Selection bias in cases may occur when degree of illness is correlated with participation rate. In this study, cases with a worse prognosis according to the Duke's classification were less likely to participate. Duke's status was related inversely to vegetable consumption: cases with Duke's C and D tumors consumed less vegetables than those with Duke's A and B tumors. If more cases with C and D tumors would have participated in the study, we might have found stronger inverse associations for vegetables. Meat consumption was not related to Duke's status in this study. Participating and nonparticipating cases did not differ

in meat consumption. Since recall of dietary habits can be influenced by a more severe prognosis or medical treatment influencing appetite, it may be an advantage to have cases with better prognosis participating in the study. Age, gender, and urbanization level of interviewed cases did not differ significantly from those eligible.

In the Netherlands, a vegetable-rich diet is related to a healthy lifestyle in general and a higher socioeconomic status. If selection of more health-conscious controls occurred, it might explain the results of this study. However, our population-based control group was comparable to the general population in distribution of socioeconomic status.

In order to minimize information bias, cases and controls were interviewed in the same season using a structured dietary-history questionnaire. Interviewers were trained by the same experienced dietitian, who intensively monitored their interviewing and coding. Each interviewer assessed dietary patterns of a similar number of cases and controls. No differences among interviewers were found.

Differential overreporting could occur if some cases remember consuming more foods in general by concentrating more intensively, which is supported by the observed positive association with total energy intake. However, adjustment for total energy intake could not explain our findings. Social desirability of eating healthy foods, such as vegetables and fruits, might influence recall as well. Since the questionnaire was structured, and the complete dietary pattern and several lifestyle variables were inquired about, it may be assumed that participants were unaware of the hypothesis tested. Moreover, the fact that no significant findings were observed for other hypotheses tested, supports that recall bias does not seem to have influenced the results importantly. Finally, changes of patterns owing to gastrointestinal distress also might be an important reason for recall bias. However, excluding those who indicated they changed their dietary patterns because of complaints did not change the results importantly.

In conclusion, selection and information bias do not seem to have distorted the internal validity of the study seriously.

Food groups of vegetable origin

With respect to vegetable consumption, our study confirms the results of the majority of other case-control studies on colon cancer which observed inverse associations with at least one vegetable group.[3] However, most studies reported nonsignificant decreases in risk by 20 to 40 percent with higher consumption of vegetables. Differences among studies might be a result of different consumption patterns among the populations studied. The consumption of vegetables in our study population is higher than in other studies, and is also high when compared with the intake among the general Dutch population, assessed using a two-day record.[36] Although checks have been included in the data entry program to compare the reported total frequency of vegetable consumption with the reported consumption of individual vegetables, this might be a consequence of the lengthy dietary-history method used.

Taking power considerations into account and the fact that the examination of a large number of food items might increase the possibility of chance findings and therefore introduce overinterpretation, we explored the associations with food groups, rather than individual food items. Previous studies observed inverse associations between colon cancer risk and green leafy vegetables[9] and cruciferous vegetables.[14] The majority of vegetables consumed in this population were cruciferous vegetables and green leafy vegetables.

Vegetable consumption was related more strongly to risk than fruits. This is not in accord with the case-control study of Steinmetz and Potter[19] conducted in Australia. In our study, an inverse association with fruit consumption was observed only among women, which is consistent with the results for fruits in other,[13,19] but not all[10] case-control studies.

Potatoes are an important source of vitamin C and polysaccharides. We observed an inverse association with potato consumption. This is in line with a few other case-control studies,[6,22] while in some studies,[12,14,19] an increased risk with potato consumption was found. Nevertheless, as potatoes often are consumed as part of the main meal, the observed inverse association might be an underestimation of the true association, because of the associated consumption of meat or the use of fat-laden condiments.

Food groups of animal origin

Except for a positive association with red meat consumption in women, only nonsignificant associations were found for food groups of animal origin. None of the quartile-specific ORs or trends were statistically significant.

A higher consumption of fish or poultry did not importantly decrease colon cancer risk as suggested by other studies.[27,29] Further, the ratio of red meat to fish and poultry was not associated with risk, which is in accord with the findings of an Australian case-control study,[29] but not with the findings in the Nurses' Health Study.[27]

Consumption of dairy products was related weakly positively, but nonsignificantly, to risk in this population.

The results of epidemiologic studies have been controversial with respect to consumption of dairy products; some[12,29,37] suggest a nonsignificant positive association, while others[11,24] observe a significant inverse association.

The consumption of eggs was not associated markedly with risk in this population. Although the range of egg consumption was similar, an Australian case-control study[29] observed an 2.4-fold increase in risk in the uppermost quartile of consumption. Cholesterol was related positively, but not significantly, to risk in our study.

An increased risk with consumption of red meat was observed among women. Beef and pork were the types of red meat most frequently consumed in this population. Increased risks with higher consumption of red meat have been observed previously in some studies,[14,16,24,27,28] but not in other ones, including a cohort study in the Netherlands.[25,26] Red meat is an important source of saturated fat which has been linked to colon cancer risk in most studies.[38] Saturated fat was associated positively, but not significantly, with risk in our study. Besides its fat content, meat might be an important source of a variety of heterocyclic amines formed during the cooking process. After enzymatic activation, these compounds are found to be potent mutagens shown to induce colon tumors.[39] Since we did not expect a large heterogeneity in meat preparation in this older population and the assessment of cooking methods might be unreliable, we did not explore methods of meat preparation in this study.

This study implies that, among women, the consumption of red meat relative to vegetables and fruits might be important. Antioxidants or other substances in vegetables and fruits might neutralize the potential initiating or promoting factors which might be present in red meat.[29]

Gender differences

Gender interactions were observed for the consumption of fruits and red meat. Different findings for men and women might make a chance finding more likely. Moreover, differences in results between genders could be due to a difference in the precision of the information on food consumption. Women, however, are more likely to give more precise information on food consumption than men; in this Dutch population, women traditionally have a more active role in food purchasing and preparation. However, to minimize recall differences between genders in our study, female spouses were asked to be present at the time of the home interview of their husbands. Another explanation for the gender differences might be related to the amount of food consumed. In this study and in the general Dutch population, women tend to consume more fruits than men. However, women consume less red meat as well.

The positive association with intake of red meat by women was mainly attributable to the reference group, with an extremely low consumption of red meat. Excluding this group from the analyses attenuated the OR. It is plausible that the category with the lowest meat consumption differs in other dietary risk factors as well. This explanation does not hold, however, since controls with the lowest red-meat consumption, compared with those with the highest, did not differ importantly for dietary variables other than animal protein (data not shown). Nevertheless, those with the lowest red-meat consumption tended to have a more health-conscious lifestyle: they smoked less, drank less alcohol, and used more vitamin supplements. Moreover, real gender differences may exist in colon cancer etiology. This is supported by the fact that men and women differ in colon physiology, such as bile acid profiles and colonic pH.[40] Moreover, epidemiologic studies have shown differences in demographic patterns of colon cancer between men and women.[41]

In summary, the results of this Dutch case-control study provide further support for a protective role of vegetable consumption in colon cancer risk. With the exception of fruits and red meat in women, they do not provide evidence for important reductions or enhancements in risk with other vegetable or animal products in the Netherlands.

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References

1. Netherlands Cancer Registry. *Incidence of cancer in the Netherlands. Second Report of the Netherlands Cancer Registry.* The Hague, Netherlands: NCR, 1990.
2. Potter JD, Slattery ML, Bostick RM, Gapstur SM. Colon

cancer: a review of the epidemiology. *Epidemiol Rev* 1993; **15**: 499-544.
3. Steinmetz KA, Potter JD. Vegetables, fruit and cancer. I. Epidemiology. *Cancer Causes Control* 1991; **2**: 325-7.
4. Block G, Patterson B, Subar A. Fruit, vegetables and cancer prevention: a review of the epidemiological evidence. *Nutr Cancer* 1992; **18**: 1-29.
5. Manousos O, Day NE, Trichopoulos D, Gerovassilis F, Tzonou A, Polychronopoulou A. Diet and colorectal cancer: a case-control study in Greece. *Int J Cancer* 1983; **32**: 1-5.
6. Macquart-Moulin G, Riboli E, Cornée J, Charnay B, Berthezène P, Day N. Case-control study on colorectal cancer and diet in Marseilles. *Int J Cancer* 1986; **38**: 183-91.
7. Kune S, Kune GM, Watson F. Case-control study of dietary etiologic factors: the Melbourne Colorectal Cancer study. *Nutr Cancer* 1987; **9**: 21-42.
8. Graham S, Marshall J, Haughey B, *et al.* Dietary epidemiology of cancer of the colon in western New York. *Am J Epidemiol* 1988; **128**: 490-503.
9. La Vecchia C, Negri E, Decarli A, *et al.* A case-control study of diet and colorectal cancer in northern Italy. *Int J Cancer* 1988; **41**: 492-8.
10. Slattery ML, Sorenson AW, Mahoney AW, French TK, Kritchevsky D, Street JC. Diet and colon cancer: assessment of risk by fiber type and food source. *JNCI* 1988; **80**: 1474-80.
11. Young TB, Wolf DA. Case-control study of proximal and distal colon cancer and diet in Wisconsin. *Int J Cancer* 1988; **42**: 167-75.
12. Tuyns AJ, Kaaks R, Haelterman M. Colorectal cancer and the consumption of foods: a case-control study in Belgium. Nutr Cancer 1988; 11: 189-204.
13. Lee HP, Gourley L, Duffy SW, *et al.* Colorectal cancer and diet in an Asian population—a case-control study among Singapore Chinese. *Int J Cancer* 1989; **43**: 1007-16.
14. Benito E, Obrador A, Stiggelbout A, *et al.* A population-based case-control study of colorectal cancer in Majorca. I. Dietary factors. *Int J Cancer* 1990; **45**: 69-76.
15. Hu J, Liyu Y, Yu Y, *et al.* Diet and cancer of the colon and rectum: a case-control study in China. *Int J Epidemiol* 1991; **20**: 362-7.
16. Bidoli E, Franceschi S, Talamini R, Barra S, La Vecchia C. Food consumption and cancer of the colon and rectum in North-Eastern Italy. *Int J Cancer* 1992; **50**: 223-9.
17. Thun MJ, Calle EE, Namboodiri MM, *et al.* Risk factors of fatal colon cancer in a large prospective study. *JNCI* 1992; **19**: 1491-500.
18. Zaridze D, Filipchenko V, Kustov V, Serdyuk V, Duffy S. Diet and colorectal cancer: results of two case-control studies in Russia. *Eur J Cancer* 1993; **1**: 112-5.
19. Steinmetz KA, Potter JD. Food-group consumption and colon cancer in the Adelaide case-control study. I. Vegetables and fruit. *Int J Cancer* 1993; **53**: 711-9.
20. Miller AB, Howe GR, Jain M, *et al.* Food items and food groups as risk factors in a case-control study of diet and colorectal cancer. *Int J Cancer* 1983; **32**: 155-61.
21. Tajima K, Tominga S. Dietary habits and gastro-intestinal cancers: a comparative case-control study of stomach and large intestinal cancers in Nagoya, Japan. *Jpn J Cancer Res* 1985; **76**: 705-16.
22. Iscovich JM, L'Abbé KA, Castelleto R, *et al.* Colon cancer in Argentina. I: Risk from intake of dietary items. *Int J Cancer* 1992; **51**: 851-7.
23. Shibata A, Paganini-Hill A, Ross RK, Henderson BE. Intake of vegetables, fruits, beta-carotene, vitamin C and vitamin supplements and cancer incidence among the elderly: a prospective study. *Br J Cancer* 1992; **66**: 673-9.
24. Peters RK, Pike MC, Garabrant D, Mack TM. Diet and colon cancer in Los Angeles County, California. *Cancer Causes Control* 1992; **3**: 457-73.
25. Goldbohm RA, van den Brandt PA, van 't Veer P, *et al.* A prospective study on the relation between meat consumption and the risk of colon cancer. *Cancer Res* 1994; **54**: 718-23.
26. Bostick RM, Potter JD, Kushi LH, *et al.* Sugar, meat, and fat intake, and non-dietary risk factors for colon cancer incidence in Iowa women (United States). *Cancer Causes Control* 1994; **5**: 38-52.
27. Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE. Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. *N Engl J Med* 1990; **24**: 1664-72.
28. Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC. Intake of fat, meat, and fiber in relation to risk of colon cancer in men. *Cancer Res* 1994; **54**: 2390-97.
29. Steinmetz KA, Potter JD. Food group consumption and colon cancer in the Adelaide case-control study. II Meat, poultry, seafood, dairy foods and eggs. *Int J Cancer* 1993; **53**: 720-7
30. Bingham SA. Diet and large bowel cancer. *J Roy Soc Med 1990;* **83**: 420-2.
31. Sorenson AW, Slattery ML, Ford MH. Calcium and colon cancer: a review. *Nutr Cancer* 1988; 11: 135-45.
32. World Health Organization. *International Classification of Disease for Oncology, First Edition.* Geneva, Switzerland: WHO, 1976.
33. Robbins SL, Cotran R. *Pathologic Basis of Disease. Second Edition.* Philadelphia, PA (USA): W.B. Saunders Co., 1979: 998.
34. *Dutch Food Composition Table 1989-90.* The Hague, Netherlands: Voorlichtingsbureau voor de Voeding, Stichting Nevo, 1989; Nevo table.
35. Willett WC, Stampfer MJ. Total energy intake: implications for epidemiological analyses. *Am J Epidemiol* 1986; **124**: 17-27.
36. *BMDP Statistical Software.* Berkeley, CA (USA): University of California Press, 1990.
37. Anonymous. *Wat eet Nederland 1987-1988*. Rijswijk, Netherlands, 1988: Ministerie van Welzijn, Volksgezondheid en Cultuur en Ministerie van Landbouw en Visserij.
38. Negri E, LaVecchia C, D'Avanzo B, et al. Calcium, dairy products and colorectal cancer. *Nutr Cancer* 1990; **13**: 255-62.
39. Turesky RJ, Lang N, Butler MA, et al. Metabolic activation of carcinogenic heterocyclic aromatic amines by human liver and colon. *Carcinogenesis* 1991; **12**: 1417-22.
40. Lampe JW, Slavin JL, Potter JD. Sex differences in colonic function: a randomized trial. *Gut* 1993; **34**: 531-6.
41. DeCosse JJ, Ngoi SS, Jacobson JS, Cennerazzo WJ. Gender and colorectal cancer. *Eur J Cancer Prev* 1993; **2**: 105-15.