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A Prospective Cohort Study on the Relation between Meat Consumption and the Risk of Colon Cancer[1]

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ABSTRACT

The high incidence of colon cancer in affluent societies has often been attributed to a high fat diet and, more in particular, the consumption of meat. The association of the consumption of meat and the intake of fat with risk of colon cancer was investigated in a prospective cohort study on diet and cancer, which is being conducted in the Netherlands since 1986 among 120,852 men and women, aged 55–69. The analysis was based on 215 incident cases of colon cancer (105 men and 110 women) accumulated in 3.3 years of follow-up, excluding cases diagnosed in the first year of follow-up. Dietary habits were assessed at baseline with a 150-item semiquantitative food frequency questionnaire.

No trends in relative rates of colon cancer were detected for intake of energy or for the energy-adjusted intake of fats, protein, fat from meat, and protein from meat. Consumption of total fresh meat, beef, pork, minced meat, chicken, and fish was not associated with risk of colon cancer either. Processed meats, however, were associated with an increased risk in men and women (relative rate, 1.17 per increment of 15 g/day; 95% confidence interval, 1.03–1.33). The increased risk appeared to be attributable to one of the five questionnaire items on processed meat, which comprised mainly sausages.

This study does not support a role of fresh meat and dietary fat in the etiology of colon cancer in this population. As an exception, some processed meats may increase the risk, but the mechanism is not yet clear.

INTRODUCTION

A number of articles have reviewed the epidemiological evidence for an association between dietary habits and the risk of colon cancer (1–4). Although the evidence seems to support a protective effect of dietary fiber and a positive effect of meat consumption and/or fat intake on colon cancer, debate remains. In case-control studies, positive associations with meat consumption or with fat intake have been found frequently, but the majority of the studies yielded nonsignificant results (5, 6). Few results are available from prospective studies, which may carry more weight than case-control studies in assessing the relation between diet and cancer since they are presumed not to be biased by recall of past dietary habits after the cancer has been diagnosed. All but two prospective studies were conducted in the United States. In Norway, Bjelke (7) found an increased relative risk for processed meat only (65 cases). In Japan, Hirayama (8) observed an increased risk of colon cancer with frequency of meat consumption in the group with infrequent vegetable consumption among a cohort of 265,000 men and women. Phillips and Snowdon (9) did not find a clear gradient in risk for frequency of meat and poultry consumption in a population of Seventh Day Adventists (139 cases), which included a large proportion of vegetarians. A prospective study among Hawaiian Japanese men (106 cases) found a negative association with (saturated) fat intake (10), but a (nonsignificant) positive association with meat consumption (11). A prospective study among female nurses showed an increased risk of colon cancer (150 cases) for the consumption of meat, in particular beef, pork, and lamb, and also for the intake of fat, in particular, saturated and monounsaturated fat (12). Quite surprisingly, the association between animal protein and the risk of colon cancer was found to be slightly inverse in this study. A comparable prospective study among middle-aged women, using a similar, although extended, dietary questionnaire, did not find an association of colon cancer (212 cases) with fat (13). In the large Cancer Prevention Study II (1150 fatal cases), no association with meat consumption or fat intake was observed (14).

We have studied the relation between meat consumption and the risk of colon cancer in the Netherlands Cohort Study, which has been initiated in 1986. Apart from meat consumption, we also included fat and protein in the analysis to obtain better insight into the origin of a possibly increased risk. Consumption of fish was included in the analysis since it is eaten instead of meat, in particular as part of the hot meal.

MATERIALS AND METHODS

The Cohort. The Netherlands Cohort Study was initiated in September 1986. The cohort included 58,279 men and 62,573 women, aged 55–69, at the start of the study. The study population originated from 204 municipal population registries throughout the country. At baseline, the cohort members completed a mailed, self-administered questionnaire on dietary habits and other risk factors for cancer. For data processing and analysis, the case-cohort approach was used; the cases were enumerated for the entire cohort, while the person years at risk accumulating in the cohort were estimated from a random sample (subcohort). This subcohort of 3500 subjects (1688 men and 1812 women) was sampled from the cohort after baseline measurement and was followed up for vital status over 3.3 years. No subcohort members were lost to follow-up. The study design has been described in detail elsewhere (15).

Follow-up for Cancer. Follow-up for incident cancer was established by computerized record linkage with all nine regional cancer registries in the Netherlands and with PALGA, a national data base of pathology reports. The method of record linkage has been published previously (16). The present analysis is restricted to cancer incidence in the period from September 1986 (baseline measurement) to December 1989, *i.e.*, a follow-up period of 3.3 years. In this period, completeness of follow-up of the cohort through linkage with the cancer registries and PALGA was estimated to be 95% (17). After excluding subjects who reported a history of cancer other than skin cancer in the baseline questionnaire, a total of 312 incident cases with microscopically confirmed primary adenocarcinoma of the colon (*i.e.*, cecum through sigmoid) were identified (157 men and 155 women).

Questionnaire. The self-administered questionnaire has been described in more detail elsewhere (18). For the present analysis, characteristics of interest are summarized below. The dietary section of the questionnaire, a 150-item semiquantitative food frequency questionnaire, concentrated on habitual intake of food and beverages during the year preceding the start of the study. The questionnaire contained 14 items on the consumption of meat with the hot meal (mainly fresh meat, including chicken), 5 items on the consumption of meat used as sandwich filling (mainly processed meat), and 3 items on fish consumption. As for the serving sizes, a question was included on the quantity of fresh meat usually purchased (per person and per meal). For processed meat, the number of sandwiches filled with each type was asked. For chicken and fish, standard serving sizes were used. Daily mean nutrient intakes were calculated using the computerized Dutch food composition table (19). Energy adjustment of nutrient intakes was done by regression analysis according to

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Table 1 *Energy, fat, and protein intake in the subcohort and colon cancer cases according to year of diagnosis*

		Men			Women		
Nutrient	Year of diagnosis	*n*	Mean	SD	*n*	Mean	SD
Energy (kcal/day)[a]							
Subcohort		1519	2159	509	1592	1688	409
Cases	1	45	1930	419	33	1723	516
	2	46	2194	435	38	1592	390
	≥3	59	2072	436	72	1673	378
Fat (g/day),size;8q[b]							
Subcohort		1519	93.7	14.4	1592	74.2	10.5
Cases	1	45	93.0	15.2	33	71.6	8.6
	2	46	93.3	12.5	38	72.8	10.7
	≥3	59	94.9	13.0	72	75.5	11.3
Protein (g/day)[b]							
Subcohort		1519	75.4	11.4	1592	65.7	10.6
Cases	1	45	72.1	10.2	33	64.3	9.0
	2	46	75.7	8.6	38	66.2	10.6
	≥3	59	74.0	9.6	72	65.5	12.0
Meat fat (g/day)[b, c]							
Subcohort		1519	19.9	8.4	1592	15.8	7.2
Cases	1	45	20.1	6.6	33	14.0	6.5
	2	46	20.1	8.6	38	15.0	8.1
	≥3	59	20.4	8.6	72	15.4	8.1
Meat protein (g/day)[b, c]							
Subcohort		1519	28.0	9.6	1592	24.0	9.0
Cases	1	45	28.9	9.5	33	21.7	8.5
	2	46	27.5	8.2	38	24.0	8.6
	≥3	59	27.7	10.3	72	23.5	9.1

[a] Age-adjusted.
[b] Age- and energy-adjusted.
[c] Meat fat and meat protein: animal fat and protein excluding dairy sources and margarine.

Willett and Stampfer (20). The questionnaire was validated against a 9-day diet record (18). Pearson correlation coefficients between mean daily intakes of energy, protein, fat, and fiber as assessed by the questionnaire and those estimated from the 9-day record were 0.70, 0.61, 0.72, and 0.74, respectively; the corresponding energy- and sex-adjusted correlation coefficients were 0.59, 0.52, and 0.74. Spearman correlation coefficients for fresh meat, processed meat, and fish were 0.46, 0.54, and 0.53, respectively.

Data Analysis. Questionnaire data of all 312 cases and the subcohort were key-entered twice and processed in a manner blinded with respect to case/cohort status in order to minimize observer bias in coding and interpretation of the data. After excluding prevalent cancer cases other than skin cancer from the subcohort, 3346 subjects (1630 men and 1716 women) remained in this group. Furthermore, subjects with incomplete or inconsistent dietary data were excluded (7.0%). Because subjects tended to skip questions on items they did not consume, questionnaires were considered incomplete when either: (*a*) more than 60 items were left blank and less than 35 items were eaten at least once a month; or (*b*) one or more item blocks (groupings of items, *e.g.*, beverages) were left blank. They were considered inconsistent when a computed cumulative score of response errors exceeded a certain value (18). Eventually, 150 male and 143 female colon cancer cases and 1525 male and 1598 female subcohort members were included in the analysis.

Fats and protein as well as animal fat and animal protein (the latter two excluding fat and protein from dairy sources and margarine) were evaluated separately. Furthermore, daily mean consumption of fresh meat (including chicken), processed meat (*i.e.*, raw and cooked, cured meat products and sausages) and fish was included in the analysis. Variables were initially included as quintile categorical variables, except fish and processed meat, which were classified into a nonuser and three user categories (0–10, 10–20, and >20 g/day). Specific types of fresh meat (beef, pork, minced meat, and chicken), and the five items on processed meat were separately investigated by including them simultaneously as continuous variables in decomposition models. Age, family history of colorectal cancer, dietary fiber intake, consumption of vegetables and fruit, and Quetelet index (kg/m^2) were considered as potential confounders.

Data were analyzed using the case-cohort approach (21), assuming exponentially distributed survival times in the follow-up period. Since standard software was not available for this type of analysis, specific programs were developed to account for the additional variance introduced by sampling from the cohort instead of using the entire cohort (17). Since subclinical symptoms of large bowel cancer might have influenced dietary habits before diagnosis, we excluded cases detected in the first year of follow-up after assessing the age- and energy-adjusted mean intake of cases diagnosed in different follow-up years. The adjusted intakes were calculated by means of analysis of covariance. After this exclusion, 105 male and 110 female colon cancer cases remained.

RESULTS

Table 1 presents mean daily intake of energy and the nutrients most relevant to this analysis for subcohort and cases categorized according to year of diagnosis. Among men, energy intake was lower in cases diagnosed in the first year of follow-up, but energy-adjusted fat intake remained fairly constant. Among women, no appreciable difference in absolute intake was detected, but energy-adjusted intake of fat and protein appeared to be lower in the cases diagnosed in the first year of follow-up. None of these differences, however, reached statistical significance. Subsequent analyses excluded cases diagnosed in the first year.

Table 2 gives the age-adjusted Pearson correlation coefficients for meats with energy intake and energy-adjusted intakes of fats, protein, and dietary fiber. Meat consumption was not strongly correlated with energy intake. The relatively high correlation of processed meat with energy could be explained by the association of bread consumption with energy. Consumption of pork and minced meat appeared to contribute most to the intake of fat, in particular, monounsaturated fat. The consumption of fresh meat and processed meat was positively associated ($r = 0.14$),[3] whereas meat and fish consumption were not related. Consumption of chicken correlated negatively with other types of meats ($r = -0.05$ to -0.13).

Table 3 displays the RRs of colon cancer for energy intake and energy-adjusted intake of fats and protein. None of the variables showed any evidence of a (positive or negative) trend across quintiles of intake. For fat and protein derived from meat, no trend

[3] The abbreviations used are: *r*, Pearson correlation coefficient; RR, relative rate; CI, confidence interval.

Table 2 *Age- and sex-adjusted Pearson correlation coefficients between meat types and intake of energy and energy-adjusted fats, protein, and dietary fiber in the subcohort*

Nutrient	Fresh meat					Fish	Processed meat
	Total	Beef	Pork	Minced[a]	Chicken		
Energy	0.23	0.10	0.15	0.10	0.04	0.10	0.33
Fat	0.21	0.03	0.19	0.14	−0.01	−0.06	0.03
Saturated	0.16	0.09	0.11	0.14	−0.06	−0.09	0.00
Monounsaturated	0.33	0.05	0.28	0.20	0.03	−0.06	0.07
Polyunsaturated	−0.04	−0.09	0.00	−0.04	0.06	0.05	0.00
Protein	0.46	0.25	0.22	0.18	0.20	0.22	0.21
Meat fat	0.67	0.15	0.59	0.44	−0.08	−0.07	0.41
Meat protein	0.83	0.39	0.53	0.26	0.28	0.31	0.38
Dietary fiber	−0.18	−0.05	−0.18	−0.06	0.01	0.02	−0.05

[a] Composed of beef and pork.

was detected either (Table 4). The pooled estimates for men and women, which were also adjusted for dietary fiber intake, did not show any association with risk either. For dietary fiber intake, a nonsignificant, slightly negative association with colon cancer was observed.

Table 5 shows the relative rates for the consumption of fresh meat (including chicken), processed meat, and fish. These data were adjusted for energy intake by including energy in the multivariate model. The results for meat were consistent with those from Table 4, *i.e.,* no evidence of a trend. Similar results were seen for frequency of meat consumption. The RRs were 0.65, 0.56, 0.78, and 0.81 for consumption frequencies of 3–4, 5, 6, and 7 days per week, respectively, relative to the reference group using meat on 0–2 days per week. Consumption of processed meat, however, showed a (nonsignificant) positive trend in men ($P = 0.06$) and women ($P = 0.10$). For fish consumption, a weakly negative but not significant association with

Table 3 *Age-adjusted RRs for quintiles of energy and energy-adjusted nutrient intakes*

Nutrient quintile	Men Median[a]	Men n[b]	Men RR	Men 95% CI	Women Median[a]	Women n[b]	Women RR	Women 95% CI	Both sexes RR[c]	Both sexes 95% CI
Energy (kcal/day)										
1	1510	23	1.00		1163	25	1.00		1.00	
2	1836	21	0.92	0.50–1.70	1435	21	0.85	0.47–1.55	0.88	0.57–1.69
3	2096	23	1.02	0.56–1.86	1626	31	1.22	0.70–2.12	1.12	0.75–1.70
4	2364	24	1.09	0.60–1.98	1848	15	0.62	0.32–1.20	0.84	0.54–1.31
5	2791	14	0.72	0.36–1.45	2200	18	0.75	0.40–1.41	0.74	0.47–1.18
P for trend			0.62				0.23		0.24	
Fat (g/day)										
1	76	20	1.00		61	24	1.00		1.00	
2	87	22	1.14	0.61–2.13	69	19	0.79	0.42–1.47	0.90	0.57–1.41
3	94	18	0.87	0.45–1.67	74	17	0.72	0.38–1.36	0.74	0.46–1.18
4	100	23	1.11	0.60–2.07	79	22	0.91	0.50–1.67	0.94	0.60–1.46
5	111	22	1.10	0.59–2.07	87	28	1.13	0.64–2.00	1.07	0.70–1.64
P for trend			0.79				0.52		0.68	
Saturated fat (g/day)										
1	28	21	1.00		23	21	1.00		1.00	
2	32	17	0.79	0.41–1.52	27	23	1.10	0.59–2.02	0.88	0.56–1.40
3	36	27	1.23	0.68–2.23	29	18	0.85	0.45–1.63	0.97	0.62–1.52
4	40	20	0.90	0.47–1.69	32	17	0.79	0.41–1.53	0.77	0.48–1.23
5	47	20	0.90	0.47–1.70	37	31	1.36	0.77–2.42	1.07	0.69–1.66
P for trend			0.88				0.51		0.91	
Monounsaturated fat (g/day)										
1	27	21	1.00		22	20	1.00		1.00	
2	32	18	0.91	0.47–1.75	25	25	1.19	0.65–2.19	0.98	0.62–1.53
3	35	21	1.03	0.55–1.93	27	24	1.15	0.62–2.14	1.01	0.64–1.59
4	38	20	0.94	0.50–1.77	30	23	1.10	0.59–2.05	0.91	0.58–1.44
5	43	25	1.26	0.69–2.31	33	18	0.88	0.45–1.69	1.00	0.63–1.57
P for trend			0.45				0.63		0.88	
Polyunsaturated fat (g/day)										
1	11	16	1.00		8	21	1.00		1.00	
2	15	20	1.20	0.61–2.37	12	20	0.99	0.53–1.86	1.04	0.65–1.67
3	18	26	1.63	0.86–3.11	14	24	1.20	0.65–2.20	1.35	0.86–2.13
4	23	19	1.17	0.59–2.32	18	19	0.99	0.52–1.91	1.04	0.64–1.69
5	31	24	1.49	0.77–2.86	24	26	1.29	0.71–2.35	1.38	0.88–2.16
P for trend			0.30				0.42		0.19	
Protein (g/day)										
1	61	19	1.00		53	23	1.00		1.00	
2	69	24	1.36	0.72–2.56	60	20	0.88	0.47–1.63	1.10	0.70–1.71
3	75	25	1.37	0.74–2.55	65	18	0.80	0.42–1.50	1.05	0.67–1.65
4	81	25	1.53	0.82–2.87	70	25	1.09	0.61–1.96	1.28	0.82–2.00
5	90	12	0.67	0.32–1.43	79	24	1.05	0.58–1.89	0.90	0.57–1.42
P for trend			0.55				0.63		0.95	

[a] Median of energy or nutrient intake in the quintile.
[b] Number of colon cancer cases in the quintile.
[c] RR also adjusted for sex and dietary fiber intake.

Table 4 *Age-adjusted RRs for quintiles of energy-adjusted intake of fat and protein derived from meat*

	Men				Women				Both sexes	
Nutrient quintile	Median (g/day)	*n*	RR	95% CI	Median (g/day)	*n*	RR	95% CI	RR[a]	95% CI
Meat fat										
1	10	24	1.00		7	24	1.00		1.00	
2	16	18	0.75	0.40–1.42	12	29	1.22	0.70–2.15	0.95	0.62–1.45
3	19	20	0.86	0.46–1.59	15	13	0.56	0.28–1.12	0.66	0.42–1.05
4	23	17	0.73	0.38–1.38	19	22	0.90	0.49–1.64	0.76	0.49–1.19
5	31	26	1.13	0.63–2.02	25	22	0.94	0.52–1.72	0.98	0.64–1.49
P for trend		0.72				0.47				0.67
Meat protein										
1	17	21	1.00		13	20	1.00		1.00	
2	23	26	1.18	0.65–2.15	20	24	1.21	0.65–2.24	1.16	0.75–1.78
3	27	18	0.87	0.45–1.67	24	22	1.05	0.56–1.97	0.91	0.58–1.44
4	32	20	0.94	0.50–1.77	28	19	0.94	0.49–1.79	0.90	0.57–1.42
5	41	20	1.00	0.52–1.90	35	25	1.24	0.68–2.29	1.07	0.69–1.67
P for trend		0.71				0.77				0.79

[a] RR also adjusted for sex and dietary fiber intake.

colon cancer occurrence was observed. Pooled results for men and women (Table 5) were also adjusted for dietary fiber intake, which had a small effect on the estimates in women. Only processed meat showed a significant ($P = 0.02$) positive trend. When fitted as a continuous variable, this resulted in a RR of 1.17 (95% CI, 1.03–1.33) for an increment of 15 g (equivalent to one sandwich filling) of mean daily consumption of processed meat. Introduction of fat from meat into the models for fresh and processed meat did not have any effect on the estimates for meat but strengthened the association between processed meat and colon cancer ($P = 0.01$).

Addition of the potential confounders [family history of colorectal cancer, consumption of vegetables and fruits, and the Quetelet index (kg/m^2)] to the models of nutrient intake and meat consumption changed the estimated relative rates in the second decimal only. Therefore, the data as presented were not adjusted for any of these variables.

The results of a further subdivision of fresh and processed meat are shown in Table 6, which displays the relative rates for an increment in consumption of 15 g/day. For fresh meats, none of the types deviated from the results for total fresh meat. For processed meat, however, "other processed meats," which mainly represented sausages, appeared to contribute most to the elevated RR.

DISCUSSION

We have presented evidence from a prospective study that the consumption of meat, fat from meat, or protein from meat is not associated with an increased risk for colon cancer. The consumption of some processed meats, in contrast, appears to be consistently and positively related to risk for colon cancer.

After excluding the cases diagnosed in the first year of follow-up, this study included 215 colon cancer cases, indicating that it had reasonable but not very large power. We thus have to take into consideration that existing associations may not have been detected only because of insufficient power. Furthermore, the validity of the food frequency questionnaire with respect to fat intake and consumption of fresh and processed meat was not very high. For (energy-adjusted) fat intake and meat consumption, this was mainly caused by the relatively small variation in intake in the population. For consumption of processed meat, which varied much more in the population studied, the relatively low correlation may be attributable to underreporting. Taking into account these limitations, there appears, nevertheless, to be a considerable difference in risk for colon cancer in this population between meat (and fat) consumption on the one hand and processed meat on the other, the latter showing a consistently increasing risk

Table 5 *RRs for fresh and processed meat and fish consumption*

	Men			Women			Both sexes	
Food group	*n*	RR[a]	95% CI	*n*	RR[a]	95% CI	RR[b]	95% CI
Fresh meat (g/day)[c]								
Q 1 (54, 43)[d]	20	1.00		24	1.00		1.00	
Q 2 (84, 72)	22	1.09	0.58–2.04	19	0.83	0.44–1.56	0.92	0.59–1.44
Q 3 (101, 91)	30	1.62	0.89–2.93	26	1.03	0.58–1.84	1.24	0.81–1.90
Q 4 (123, 107)	18	0.98	0.51–1.91	22	1.05	0.57–1.93	0.98	0.62–1.55
Q 5 (158, 145)	15	0.87	0.43–1.77	19	0.88	0.45–1.69	0.84	0.51–1.37
P for trend		0.70			0.97		0.62	
Processed meat (g/day)								
0	9	1.00		14	1.00		1.00	
0–10	30	1.25	0.59–2.70	44	1.22	0.66–2.26	1.23	0.76–1.98
10–20	29	1.45	0.67–3.12	30	1.48	0.77–2.87	1.43	0.87–2.35
>20	37	1.84	0.85–3.95	22	1.66	0.82–3.35	1.72	1.03–2.87
P for trend		0.06			0.10		0.02	
Fish (g/day)								
0	34	1.00		36	1.00		1.00	
0–10	28	0.84	0.50–1.42	25	1.14	0.67–1.94	1.00	0.68–1.47
10–20	11	0.41	0.21–0.83	22	1.14	0.66–1.97	0.74	0.48–1.15
>20	32	0.73	0.44–1.21	27	0.87	0.52–1.45	0.81	0.56–1.17
P for trend		0.09			0.64		0.14	

[a] Age (year) and energy included in model as continuous variables.
[b] RR also adjusted for sex and dietary fiber intake.
[c] Including all types of meat (except processed meat) and chicken.
[d] Medians of the consumption (g/day) in each quintile for men and women, respectively.

Table 6 *Mean, SD, and age- and energy-adjusted RRs for types of fresh and processed meat, fitted as continuous variables*

Type	Model[a]	Mean (g/day)	SD (g/day)	RR[b]	95% CI
Total fresh meat	a	99	42	0.98	0.93–1.03
Beef	b	25	22	0.96	0.87–1.06
Pork	b	38	30	0.99	0.92–1.06
Minced meat [c]	b	18	17	0.91	0.80–1.04
Liver	b	2	4	0.90	0.54–1.48
Chicken	b	14	16	1.03	0.90–1.17
Other meat	b	3	6	0.99	0.66–1.47
Total processed meat	c	14	16	1.17	1.03–1.33
Ham	d	4	7	1.04	0.78–1.39
Bacon[d]	d	1	4	1.25	0.84–1.88
Lean meat products[d]	d	3	5	1.14	0.82–1.61
Cooked liver	d	1	2	0.15	0.02–1.12
Other processed meats[f]	d	5	8	1.27	1.04–1.55

[a] Models were fitted for: (*a*) total fresh meat; (*b*) fresh meat decomposed in types; (*c*) total processed meat; and (*d*) processed meat decomposed in types. All models were adjusted for sex, age, and energy. LR-χ^2 for the (combined) meat terms: 0.99, 3.33, 5.77, and 11.13 for models *a* to *d*, respectively.
[b] RR per increment of 15 g/day, equivalent to one standard sandwich filling.
[c] Composed of beef and pork.
[d] Raw, cured belly and dried backs.
[e] Raw, cured smoked beef, lean cooked ham, and lean cooked pork.
[f] Mainly sausages.

with increasing consumption in men as well as women. The consumption of fresh meat and specific types of meat (beef, pork, minced meat, and chicken), in contrast, does not display any trends in risk, while the RR for those in the highest quintile is lower than unity most of the time.

The follow-up period of 3.3 years in this study is rather short. As a consequence, subclinical disease that caused a change in dietary habits may have been present in a relatively large proportion of the cases at baseline. We dealt with this problem by excluding all cases diagnosed in the first year of follow-up. Another issue is the supposedly short latency period between baseline measurement and diagnosis. However, a reproducibility study, in which the food frequency questionnaire was readministered annually during 5 years after baseline assessment, showed that within subjects, dietary intake remained fairly stable over time.[4] These results imply that the baseline questionnaire addressed an earlier and longer period in the subjects' lives than just the preceding year.

Detection bias may be another concern in colon cancer studies. In the Netherlands, however, mass screening of symptomless subjects for colorectal cancer does not take place, neither by hemoccult tests nor by colonoscopy. Apart from family members of patients with hereditary colorectal cancer, a first colonoscopy is only performed in patients with gastrointestinal complaints but may be repeated if those patients appeared to have polyps or a positive first degree family history of colorectal cancer. For 60% of the cases in this study, data on the pathological stage of disease (TNM) were available. For fat intake and fresh meat consumption the size of the tumor (T_1 and T_2 *versus* T_3 and T_4) did not differ between high and low categories of intake, whereas for processed meat, the consumers in the two lowest categories appeared to be diagnosed on average in an earlier stage than those in the two highest consumption categories. The latter finding would thus have increased the apparent incidence rate in the reference group and cannot, therefore, explain the increased relative risk for processed meat.

We also have to consider the possibility that the results can be explained by confounding by dietary or other determinants of colon cancer. However, we have adjusted for intake of dietary fiber, which resulted in marginally changed relative rate estimates. No effect of the other evaluated potential confounders on the estimates was observed. Other nutrients were no or only weak determinants of colon cancer. Smoking and alcohol consumption have also been shown to be hardly related to colon cancer in this data set (22). We cannot entirely exclude, however, the possibility that residual confounding or an unevaluated confounder (*e.g.*, physical activity) have had some effect on the results.

Comparing our results with the findings of others, we may conclude that those for (fresh) meat are in agreement with the substantial number of epidemiological studies showing no association (7, 9, 10, 14, 23–29). The consumption of processed meat has been investigated in a smaller number of studies than those on meat in general (7, 9, 12, 14, 23, 24, 27–37). Most of these studies, however, did not find an increased risk for (types of) processed meat, with the exceptions of Bjelke (7), Young and Wolfe (29) (for lunchmeat only), Willett *et al.*(12), and Thun *et al.* (14). This does not necessarily mean that our finding for processed meat is a chance finding. Processed meat differs from fresh meat in that it has been cured with the addition of preservatives (salt, nitrite, and smoke) and other additives (phosphate, glutamate, and ascorbic acid). In the Dutch population, fresh meat, usually beef, pork, minced meat, chicken, or fish are part of the hot meal, which is taken once per day and further includes vegetables and (usually) potatoes. Processed meat, on the other hand, may or may not constitute part of the sandwich meals, which are taken by most people twice daily. It may be that, in this population, the circumstances in which processed meats are eaten, as a sandwich without vegetables and often without fruits in the same meal, are important determinants for the risk. Unfortunately, we do not yet have a sufficient number of cases to explore these possibilities.

The conflicting results between studies regarding meat consumption and colon cancer risk may be attributable to a number of sources: (*a*) the validity of the dietary questionnaire may have been insufficient in some studies. This is critical, in particular, when the variability in the study population with respect to meat consumption and fat intake is small; (*b*) the average age of the study population differed between studies. Available evidence suggests that associations may be stronger at younger ages (7). This may be one of the explanations for the positive result in the Nurses' Health Study, which is based on a relatively young cohort (12); (*c*) risk of colon cancer may depend on the method of preparation of the meat (products), which is likely to differ between populations. Gerhardsson de Verdier *et al.* (34) observed an increased risk for subjects who preferred meat with a heavily browned surface. This could be explained by the formation of mutagenic and carcinogenic heterocyclic amines at high temperatures (38). In epidemiological studies, however, there appears to be no clear relationship between risk and the temperature at which meat is prepared (29, 34, 39). We did not inquire about methods of meat preparation in our study, but in this country it is usually pan-fried or stewed; and (*d*) last but not least, one of the most promising explanations is the population level of and variability in the consumption of other foods, such as (specific) vegetables, which may modify the effects of meat consumption (8, 40, 41). Large studies are required, however, to study effect modification in a relatively homogeneous population.

We conclude from the data presented here that our prospective study does not support the hypothesis that a higher consumption of (fresh) meat increases the risk of colon cancer within the range of meat consumption and fat intake prevailing in the population studied. Consumption of some processed meats, on the other hand, may increase risk for colon cancer in this population. These results warrant further analysis, in particular in combination with other foods and nutrients, when, after more years of follow-up, more cases have been accumulated.

[4] R. A. Goldbohm, P. van 't Veer, P. A. van den Brandt, M. A. van 't Hof, H. A. M. Brants, F. Sturmans, and R. J. J. Hermus. Reproducibility of a food frequency questionnaire and stability of dietary habits determined from five annually repeated measurements, submitted for publication.

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