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Dietary Risk Factors for Cancer and Adenomas of the Large Intestine. A Case–control Study Within a Screening Trial in Denmark

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The aims of the study were to estimate the importance of dietary habits for colorectal cancers and adenomas. By comparing risk factors among cancer and adenoma patients the adenoma cancer theory was indirectly evaluated. The study was performed as a case–control study within a large screening trial in Denmark. All cancer and adenoma patients diagnosed at the screening were recruited as cases; controls were selected among test negatives after matching for age, sex and time of screening. All those selected except 85, participated in a 7-day dietary recall. Altogether 49 colorectal cancer patients and 172 with adenomas were examined; 362 individuals who were test negatives in the Hemoccult-II screen served as controls. The intake of crude dietary fibres was shown to be associated with reduced risk of cancer as well as adenomas. Neither cancer nor adenoma occurrences were related to total energy intake or body mass. Vitamins E and A were negatively associated with adenoma occurrence.
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INTRODUCTION

COLORECTAL CANCER is one of the five most common cancers in Denmark for males and females [1]. Screening programmes for this cancer are under evaluation but primary prevention may also be an option when we have solid knowledge on avoidable cancers. Epidemiological evidence points towards diet as a risk factor for the development of cancer and to some extent this is supported by animal experiments [2]. Register linkage studies have not shown an association between the risk of colorectal cancer in spouses [3] but have shown a weak association between parents and children [4]. This may indicate a genetic component to the aetiology and to some extent weakens the argument for a role of diet, assuming that dietary habits correlate more closely between spouses than between parents and their children. This need not, however, be true.

For theoretical as well as practical purposes, more knowledge about the steps in colorectal carcinogenesis is needed. Secondary prevention, by removing colorectal polyps, is based upon the assumption that the adenoma carcinoma sequence is true [5]. On the other hand, it is likely that there is no unique pathway to malignancy, and cancers of the colon may develop from loss of gene function on chromosome 5 [6]. If, however, adenomas and colorectal cancers share some common aetiology it suggests that adenomas are the precursors of cancer.

The epidemiological literature points towards an association between fat, dietary fibres and colorectal cancer but more studies are needed, especially those that overcome recall bias problems in case–control studies due to the influence of the disease state on appetite and perceived dietary habits. Most case–control studies on risk factors for colorectal cancer have collected data at a stage when the cancer was known to the patients and may, therefore, be biased because of incomparability of information among cases and controls. In the present study, the dietary assessment was made at a very early, still undiagnosed, stage of the cancer. If some adenoma patients go on to develop cancer they may serve as very early reporters of possible component causes, at a stage where the disease has had little chance to affect dietary habits. Furthermore, the study aimed to explore the adenoma carcinoma theory by comparing dietary risk factors in the adenoma and carcinoma groups. If adenoma represents an early stage in the development of cancer one would expect the two types of lesions to share common aetiologic factors.

MATERIALS AND METHODS

The study was conducted as a case–control study within a randomised control trial for colorectal cancer with Hemoccult-II on the island of Funen, Denmark. Almost half of the population in the area between 45 and 74 years of age were enrolled in the trial, of which 30 970 were randomised to screening and 30 968 to the control group. In the first screening in 1986, 20 672 participated, 18 179 in the second screening in 1988 and 17 284 in the third screening which took place in 1990. All patients with known colorectal cancer and adenoma were

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removed from the study base before randomisation. A complete colonoscopy was obtained in more than 85% of those giving a positive screening test. A more detailed description of the screening trial is found in [7, 8].

As part of the screening programme, a 7-day dietary recall was collected by a trained nutritionist on all those with a positive screening test and on an age- and sex-matched control, taken from the screened group with a negative Hemoccult-II test within the same day of testing. Cases were later identified as test positives with a diagnosis of cancer or adenoma, and controls were test negatives. The interviews were also conducted before cases or controls received the result of the screening test but 33 controls were excluded because an appointment could not be made in time. Two interviewers were involved in the data collection but one interviewer conducted all the dietary recalls in the second and the third screening. The first part of the first screening was used to pilot the study and only participants from the second half of the first screening were included in the analyses.

The dietary interviewing was conducted by telephone according to standardised questionnaires using colour photographs (sent out beforehand) to illustrate portion sizes. Only six people refused to participate in the interview, 43 could not be interviewed in time (all from the first screening) and 36 left the study for other reasons (could not be contacted, died, left the region, etc.). All dietary data were processed in the same database (Dankost) and all analyses were based on estimated nutritional output data from the database. Previous use of the dietary questionnaire has been described [9–12].

Since the matching was performed in order to select between several potential controls, and since the final selection of cases and controls did not follow the first step of sampling, analyses of variance and logistic regression were performed on the unmatched data but were adjusted for the matching factors, age and sex. When adjusting for total energy intake, total energy was included in the analyses of variance with the 'energy-adjusted' nutrient term. The 'energy-adjusted' nutrition term was computed as residuals from the regression model with total energy as the independent variable and absolute nutrient intake as the dependent variable [13, 14]. The Body Mass Index (BMI) was computed as the weight (kg) divided by height (m) and it is based upon self-reported data. Minor differences in the number of patients/controls available for each variable occurred due to missing data.

Descriptive data for the people who participated in the interview are presented in Table 1. Among cancer patients 42% were female, 34% were females in the group of adenomas, 49% had other diagnoses, and 44% were not tested or were without a diagnosis. All groups had a mean age of 60–68 years. Cancer patients were on average 66.6 years of age (S.D. 7.2), adenoma patients 64.4 years (S.D. 7.5), other diagnoses 62.7 years (S.D. 8.2), and the not-tested or people without a diagnosis 63.4 years (S.D. 8.2).

Table 1. Descriptive data for the participants

Variables	Number	%
Participated in first screening	160	21
Participated in second screening	306	40
Participated in third screening	293	39
Sex		
Female	321	42
Male	438	58
Age at screening (years)		
45–49	23	3
50–54	105	14
55–59	115	15
60–64	136	18
65–69	166	22
70–74	127	17
⩾ 75	87	11
Diagnoses		
Colon cancer	32	4
Rectal cancer	17	2
Colon adenomas	154	20
Rectal adenomas	18	2
Other diagnoses	104	14
No diagnose/not tested positive	434	57

*Table 2. Body mass index (BMI) and dietary components among 49 colorectal cancer cases and 362 negative controls. Analyses of variance adjusted for age, sex and energy intake**

Variable		Mean	S.D.	*P* value analyses of variance
BMI	Cases	25.9	4.8	0.93
(kg/m²)	Controls	25.3	3.7	
Energy	Cases	7641	2047	0.55
(kJ)	Controls	7803	2499	
Total	Cases	81.8	27.6	0.88*
fat (g)	Controls	83.6	31.6	
Saturated	Cases	33.8	12.0	0.25*
fat* (g)	Controls	33.5	13.6	
Polyunsaturated	Cases	12.1	5.7	0.72*
fat (g)	Controls	12.6	5.8	
Dietary fibre	Cases	17.4	6.8	0.11*
(g)	Controls	19.3	7.3	
Vitamin A	Cases	1432	1000	0.54*
(μg)	Controls	1363	1103	
Vitamin C	Cases	79.1	46.2	0.41*
(mg)	Controls	75.0	45.7	
Vitamin D	Cases	2.8	1.8	0.81*
(μg)	Controls	3.0	2.5	
Vitamin E	Cases	6.0	2.9	0.48*
(mg)	Controls	6.5	4.8	

A full dietary interview was missing for 54 persons (4 cases and 50 controls). * Analyses included intake and residuals from the regression of the nutrition with total energy.

RESULTS

Cancer patients

Table 2 shows little difference in BMI or energy intake between colorectal cancer patients and controls. A large variance was noted in energy intake. Neither total fat, saturated fat nor polyunsaturated fat intake was higher on average for the cancer patients than for the controls. The findings were similar for the 32 colon cancer patients, except for polyunsaturated fat intake, being on average 3 g lower among cancer patients ($P = 0.30$).

The total intake of fibre was found to be about 1.9 g less among cases than controls [and 2.3 g less for colon cancer patients ($P = 0.04$)]. For rectal cancer patients the adjusted intake of vitamin A was 430 μg higher among controls ($P = 0.09$), and vitamin C 17 mg higher among cases

(P = 0.09). Saturated fat intake was 2.8 g higher among rectal cancer patients than controls (P = 0.10).

None of the intakes of the vitamins listed in Table 2 differed greatly between colorectal cancer patients and controls. Similar findings were seen for colon cancer patients only.

The reported alcohol intake was similar in both cancer groups and among controls (data not shown).

In Table 3, the results of logistic regression performed on data categorised in tertiles are shown. All results have been repeated for colon cancer patients and rectal cancer patients separately (data not shown). No association was found betweeen BMI, energy intake and colorectal cancer. For colon cancer patients crude odds ratios (OR) for BMI were 1.0, 1.4 and 2.1 (no statistically significant trend) and for energy ORs were 1.0, 0.9 and 0.8. No association was found for total fat and colorectal cancer (the same was true for colon cancer patients). The

Table 3. Odds ratios (ORs) for colorectal cancer according to tertiles of body mass index (BMI) and dietary components. Logistic regression adjusted for age (in years), sex and energy intake

Variables	Tertiles 1	2	3	Adjusted ORs (95% C.I.) 1	2	3
BMI (kg/m²)						
Range	16.4–23.7	23.8–26.5	26.6–43.9			
Cases	16	12	19			
Controls	122	123	110	1.0	0.68	1.18
Unadjusted OR	1.0	0.74	1.32	-	(0.3–1.5)	(0.6–2.5)
Energy (kJ)						
Range	1751–6576	6577–8411	8412–16510			
Cases	15	13	17			
Controls	96	106	110	1.0	0.71	0.89
Unadjusted OR	1.0	0.78	0.99	—	(0.3–1.6)	(0.4–2.1)
Total fat (g)						
Range	16–65	66–89	90–244			
Cases	13	16	16			
Controls	94	101	117	1.0	1.14	0.96
Unadjusted OR	1.0	1.15	0.99	—	(0.5–2.5)	(0.4–2.2)
Saturated fat (g)						
Range	5–25	26–35	36–91			
Cases	10	17	18			
Controls	95	94	123	1.0	1.73	1.32
Unadjusted OR	1.0	1.72	1.39	—	(0.7–4.0)	(0.6–3.1)
Polyunsaturated fat (g)						
Range	3–8	9–12	13–48			
Cases	13	16	16			
Controls	81	91	140	1.0	1.00	0.64
Unadjusted OR	1.0	1.10	0.71	—	(0.5–2.3)	(0.3–1.5)
Dietary fibre (g)						
Range	5–14	15–19	20–58			
Cases	17	15	13			
Controls	74	114	124	1.0	0.54	0.42
Unadjusted OR	1.0	0.57	0.46	—	(0.2–1.2)	(0.2–0.9)
Vitamin A (μg)						
Range	194–806	807–1370	1371–5840			
Cases	10	19	16			
Controls	109	99	104	1.0	1.96	1.67
Unadjusted OR	1.0	2.09	1.68	—	(0.9–4.5)	(0.7–3.9)
Vitamin C (mg)						
Range	9–48	49–78	79–351			
Cases	14	10	21			
Controls	98	102	112	1.0	0.71	1.35
Unadjusted OR	1.0	0.68	1.31	—	(0.3–1.7)	(0.6–2.8)
Vitamin D (μg)						
Range	0–1	2	3–42			
Cases	8	18	19			
Controls	50	121	141	1.0	0.94	0.81
Unadjusted OR	1.0	0.93	0.84	—	(0.4–2.3)	(0.3–2.0)
Vitamin E (mg)						
Range	1–4	5	6–21			
Cases	17	8	20			
Controls	81	55	176	1.0	0.68	0.51
Unadjusted OR	1.0	0.69	0.54	—	(0.3–1.7)	(0.2–1.1)

A full dietary interview was missing for 54 persons (4 cases and 50 controls). C.I., confidence interval.

association between colorectal cancer and saturated fat, as well as polyunsaturated fat, did not show any clear trend and was not statistically significant (ORs for colon cancer patients were only 1.0, 1.1 and 1.2 for saturated fat, and for polyunsaturated fat 1.0, 0.8 and 0.6; this was not a statistically significant trend).

The intake of crude dietary fibres showed a protective effect for colorectal cancer with a statistically significant trend ($P = 0.04$). The association was most marked for colon cancer patients with ORs of 1.0, 0.4 and 0.4 (test for trend $P = 0.03$).

The most apparent association between vitamin intake and colorectal cancers was found for vitamins D and E. However, none of the associations was statistically significant at the 0.05 level. For colon cancer patients, the ORs for vitamin A were 1.0, 1.7 and 1.2; for vitamin C: 1.0, 0.4 and 0.9; for vitamin D: 1.0, 0.9 and 0.9; and for vitamin E: 1.0, 0.5, 0.4. The last association had a statistically significant trend ($P = 0.04$).

The results in Table 4 are energy-adjusted in the sense that the proportional distribution of the total energy according to specific components is presented. None of the findings reach statistical significance; however, tendencies for protective effects from carbohydrates and the ratio of unsaturated fat to saturated fat are seen. Among colon cancer patients, these tendencies were less marked (ORs for carbohydrate = 1.0, 1.0 and 1.1, and unsaturated fat to saturated fat ratio = 1.0, 0.75 and 0.8). For total fat and protein, results were similar to those for colorectal cancers.

By dichotomising the intake of crude dietary fibres in g/MJ (at the median), the high values had an OR for colorectal cancer of 0.64 (for colon cancer 0.48). None of these findings reached statistical significance. The amount of essential fatty acids as a percentage of total fat was not associated with either colorectal cancer or colon cancer.

Adenoma patients

Table 5 shows results for adenoma patients which are similar to those presented for cancer patients in Table 2. The intake of polyunsaturated fat, dietary fibre and vitamin E was significantly lower among adenoma patients compared with controls, but was similar to that found for cancer patients (Table 2). The daily alcohol intake in adenoma patients was reported to be 6 g lower than for controls (not statistically significant).

Table 6 presents results for adenoma patients similar to those shown for cancer patients in Table 3. The table indicates a protective effect mainly from crude dietary fibres, but also from polyunsaturated fat and vitamin E. The test for trend also showed a protective effect from vitamin A intake ($P < 0.05$).

Table 7 displays results for adenoma patients similar to those presented in Table 4 for the cancer group. None of the findings reach statistical significance except for the ratio of unsaturated fat to saturated fat. The findings here are similar to those seen for cancer patients. The intake of essential fatty acids appeared to be lower among adenoma patients than controls (OR = 0.53; confidence interval 0.3–0.8, when data were dichotomised at 1% of total energy intake) and the proportion of total energy from alcohol was statistically significantly higher among cases than controls.

DISCUSSION

This study corroborates the hypothesis that the intake of fibre protects against colorectal cancers [15]. It gives some support to the idea that vitamin E also has protective effects (especially against colon cancer) and that saturated fat may be casually linked with cancer, but the cancer case group is small and the amount of information limited. The study does to some extent detract from the hypothesis that the link between colorectal

Table 4. Odds ratios (ORs) for colorectal cancer according to tertiles of the relative distribution of dietary characteristics. Logistic regressions adjusted for age (in years) and sex

Variables	Tertiles 1	2	3	Adjusted ORs (95% C.I.) 1	2	3
Fat (% of total energy)						
Range	15–37	38–42	43–62			
Cases	13	12	20			
Controls	95	95	122	1.0	0.90	1.13
Unadjusted OR	1.0	0.92	1.20	—	(0.4–2.1)	(0.6–2.5)
Protein (% of total energy)						
Range	7–11	12–14	15–32			
Cases	11	16	18			
Controls	60	155	96	1.0	0.63	1.23
Unadjusted OR	1.0	0.56	1.02	—	(0.3–1.5)	(0.5–2.9)
Carbohydrate (% of total energy)						
Range	13–38	39–44	45–69			
Cases	14	20	11			
Controls	76	119	116	1.0	0.81	0.43
Unadjusted OR	1.0	0.91	0.52	—	(0.4–1.7)	(0.2–1.0)
Ratio of polyunsaturated fat/saturated fat						
Range	0–2.1	2.2–3.8	3.9–10.0			
Cases	19	11	15			
Controls	100	97	114	1.0	0.56	0.68
Unadjusted OR	1.0	0.60	0.69	—	(0.3–1.2)	(0.3–1.4)

A full dietary interview was missing for 54 persons (4 cases and 50 controls). C.I., confidence interval.

*Table 5. Body mass index (BMI) and dietary components among 172 ademona cases and 362 negative controls. Analyses of variance adjusted for age, sex and energy intake**

Variable	Mean	S.D.	*P* value analyses of variance
BMI (kg/m²)			
Cases	25.4	3.6	0.73
Controls	25.3	3.7	
Energy (kJ)			
Cases	7848	2418	0.41
Controls	7802	2499	
Total fat (g)			
Cases	81.9	29.5	0.17*
Controls	83.6	31.7	
Saturated fat (g)			
Cases	33.2	13.3	0.79*
Controls	33.4	13.6	
Polyunsaturated fat (g)			
Cases	11.6	5.2	0.00*
Controls	12.6	5.8	
Dietary fibre (g)			
Cases	18.2	7.3	0.04*
Controls	19.3	7.3	
Vitamin A (μg)			
Cases	1171	787	0.06*
Controls	1363	1104	
Vitamin C (mg)			
Cases	75.2	44.8	0.76*
Controls	74.2	45.7	
Vitamin D (μg)			
Cases	2.7	1.4	0.18*
Controls	3.0	2.6	
Vitamin E (mg)			
Cases	5.6	2.5	0.02*
Controls	6.5	4.8	

A full dietary interview was missing for 69 persons (19 cases and 50 controls). * Analyses included residuals from the regression of the nutrition with total energy.

Table 6. Odds ratios (OR) for colorectal adenomas according to tertiles of body mass index (BMI) and dietary components. Logistic regressions adjusted for age (in years), sex and energy intake

Variable	Tertiles 1	2	3
BMI (kg/m²)			
Cases	59	57	52
Controls	122	123	110
Unadjusted OR	1.0	0.96	0.98
Adjusted OR	1.0	0.86	0.87
95% C.I.	—	0.5–1.4	0.6–1.4
Energy (kJ)			
Cases	45	53	54
Controls	96	106	110
Unadjusted OR	1.0	1.07	1.05
Adjusted OR	1.0	0.86	0.77
96% C.I.	—	0.5–1.5	0.4–1.3
Total fat (g)			
Cases	46	56	50
Controls	94	101	117
Unadjusted OR	1.0	1.13	0.87
Adjusted OR	1.0	1.03	0.71
95% C.I.	—	0.6–1.7	0.4–1.2
Saturated fat (g)			
Cases	43	55	54
Controls	95	94	123
Unadjusted OR	1.0	1.29	0.97
Adjusted OR	1.0	1.21	0.83
95% C.I.	—	0.7–2.0	0.5–1.4
Polyunsaturated fat (g)			
Cases	49	47	56
Controls	81	91	140
Unadjusted OR	1.0	0.85	0.66
Adjusted OR	1.0	0.74	0.50
95% C.I.	—	0.4–1.2	0.3–0.8
Dietary fibre (g)			
Cases	57	47	48
Controls	74	114	124
Unadjusted OR	1.0	0.54	0.50
Adjusted OR	1.0	0.45	0.39
95% C.I.	—	0.3–0.8	0.2–0.7
Vitamin A (μg)			
Cases	63	48	41
Controls	109	99	104
Unadjusted OR	1.0	0.84	0.68
Adjusted OR	1.0	0.79	0.65
95% C.I.	—	0.5–1.3	0.4–1.1
Vitamin C (mg)			
Cases	52	48	52
Controls	98	99	115
Unadjusted OR	1.0	0.89	0.88
Adjusted OR	1.0	0.86	0.86
95% C.I.	—	0.5–1.4	0.5–1.4

Continued.

cancers and dietary factors is due to an energy effect. Neither total energy nor BMI was associated with colorectal cancers.

A number of limitations must be taken into consideration when interpretating the data. The cancer group was small and a 7-day recall of diet outside the proper exposure time period certainly introduces substantial misclassification, and bias and unbiased estimates of risk factors could in fact be much larger. It is also possible that the dietary restrictions preceeding the Hemoccult-II test could have had an impact on the 7-day dietary recall which appears a little low, even in this group of elderly patients. Such a bias should, however, be of the same magnitude for cases and controls.

Problems with colinearity exist not only between total energy intake and dietary components but also between separate dietary items (the correlation between total energy intake and fat was in the same range as reported elsewhere [16]). Epidemiological studies may help to identify areas where one should look for protective or preventive components but these are not well suited for identifying the components themselves.

Only a limited number of cancer cases were available for study and further subclassification of ORs according to anatomic site-specific associations is not possible. The epidemiology of colorectal cancers makes it likely that site-specific associations will differ [17]. Fats have been shown to increase the risk of cancer of the ascending colon and proteins to increase the risk of cancers of the descending colon in males [18].

It would also have been desirable to stratify the data on specific screens and stratification on screenings was applied in the data analyses but did not produce noticeably different results. However, the detection level of heterogeneity across screenings is low. In all screenings prevalent cancer cases were detected,

Table 6. Continued

Variable	Tertiles 1	2	3
Vitamin D (μg)			
Cases	23	65	64
Controls	50	121	141
Unadjusted OR	1.0	1.17	0.99
Adjusted OR	1.0	1.10	0.85
95% C.I.	—	0.6–2.0	0.5–1.5
Vitamin E (mg)			
Cases	57	26	69
Controls	81	55	176
Unadjusted OR	1.0	0.67	0.56
Adjusted OR	1.0	0.62	0.48
95% C.I.	—	0.3–1.1	0.3–0.8

A full dietary interview was missing for 70 persons (20 cases and 50 controls). C.I., confidence interval.

but after the first screening, the cases represented cancer which had either developed to a level of detection in the screening interval, or had a negative screening test at the previous screen. Furthermore, cancer patients diagnosed during this time by normal clinical detection were not included.

The adenoma cancer hypothesis is only partly supported by the data. The dietary habits of adenoma patients were more similar to those of cancer patients than those of controls. Adjusted crude fibres and vitamin E showed protective effects (Tables 3 and 6), and with values within confidence limits of the case group.

The main problem in studying dietary factors in cancer research is to get accurate exposure data for the relevant time period during disease causation. Obviously, case–control studies have severe shortcomings in this respect. The rationale behind this type of research is that the ranking of respondents according to present dietary habits is associated with the relevant ranking years before the diagnosis. Since data are not collected from the appropriate time period, the results are only presented according to the composition of the diet in summary fractions. Specific intakes of meat, fruit and vegetables may have changed substantially over the years and are, therefore, not reported in the present study. The intake of fibre is given as a total intake of fibre from all sources (mainly from vegetables and bread), as the computer programme used in the first screen did not distinguish between different types of fibre. Unfortunately, data are not available for analysing the fibre intake by source of grain, fruit or vegetable.

The largest, and probably the best, study on dietary factors and colon cancer like this study, showed no association between total energy intake and BMI and colon cancer [19]. The study showed a significant association with total fat, unlike the findings here; however, the results concerning saturated fat are rather similar. Their reported association with dietary fibre was weaker than in this study but with the same trend.

The intake of cruciferous vegetables has been shown to be negatively associated with colorectal cancers [20], and the association between dietary fibre and colorectal cancer need not reflect a causal link between fibre and cancer but could be due to confounding by other potential protective factors associated with fibre intake. Fibre intake from vegetables was found to be negatively associated with rectal cancers in a case–control study

Table 7. Odds ratios (OR) for colorectal adenomas according to tertiles of dietary components. Logistic regression adjusted for age (in years) and sex

Variables	Tertiles 1	2	3
Fat (% of total energy)			
Cases	53	48	51
Controls	95	95	122
Unadjusted OR	1.0	0.91	0.75
Adjusted OR	1.0	0.93	0.75
95% C.I.	—	0.6–1.5	0.5–1.2
Protein (% of total energy)			
Cases	40	70	42
Controls	60	155	96
Unadjusted OR	1.0	0.68	0.66
Adjusted OR	1.0	0.69	0.71
96% C.I.	—	0.4–1.1	0.4–1.2
Carbohydrate (% of total energy)			
Cases	33	65	54
Controls	76	119	116
Unadjusted OR	1.0	1.26	1.07
Adjusted OR	1.0	1.26	1.12
95% C.I.	—	0.8–2.1	0.7–1.9
Ratio of polyunsaturated fat/saturated fat			
Cases	58	53	41
Controls	100	97	114
Unadjusted OR	1.0	0.94	0.62
Adjusted OR	1.0	0.92	0.58
95% C.I.	—	0.6–1.5	0.4–0.9

A full dietary interview was missing for 70 persons (20 cases and 50 controls). C.I., confidence interval.

from New York. Similarly, carotenoids and vitamin C were negatively associated with rectal cancers [21].

The combined amount of information from all these studies points towards the association between intake of vegetables and fruits and a reduced risk of cancers of the alimentary tract [22]. The present findings could reflect such an association. Studies on dietary fibre and colorectal cancer have not shown consistent findings [23], probably because only specific types of fibre play a protective role or because intake of fibre is correlated with other nutrients.

The association between saturated fat and colorectal cancer (or the protective effect of unsaturated fat) is supported by the link between serum cholesterol, β-lipoprotein and colorectal cancers, found in a large follow-up study in Sweden. Animal studies have shown that the type of fat and fatty acid composition play a role, perhaps through their elevation of agents that act as promoters of tumour development [25, 26].

The Hemoccult test does not detect all cancer and certainly not all adenomas. The later medical examination ensures a high specificity but the sensitivity is certainly less than one, especially for the adenomas. This reduces the amount of information in the study but does not bias the ratio measures of association. It must also be anticipated that the controls are not necessarily without the diseases under study, especially not without adenomas. This will, to some extent, reduce the statistical precision in the study but not necessarily bias the measure of association, as long as the reference group produces an unbiased estimate of dietary habits in the study base.

It is possible that the results are due to confounding. Only little is known about the causes of colorectal cancers or adenomas but adjustment for coffee drinking, smoking and exercise did not affect the results appreciably. Confounding due to unmeasured components of the diet is probably a much greater problem.

The lack of clustering of colorectal cancers in husband–wife pairs has been taken as evidence against the importance of the dietary factors in cancer occurrence, but could be due to the early effect of dietary factors in childhood or adolesence, or the lack of an association between dietary intake in families. An association between colorectal cancer risks in parents and their children would to some extent support this hypothesis. However, one study conducted in Hawaii showed no major differences between husband and wife nutrient intake, except for vitamin A and C [27], but such findings may not be valid for other populations.

For obvious reasons, no epidemiological dietary studies have been conducted on unselected adenoma patients. The selection criteria in this study were participation in the screening programme and bleeding which could be detected at screening; thus, it is unknown if the findings represent causes of adenomas or causes of bleedings. Comparing test positives with a diagnosis to test positives without a diagnosis did not reveal findings very different from those presented. A small study on a population of 400 persons, who were screened for rectosigmoidal polyps, showed a low fibre intake among polyp patients and a high intake of fat and cruciferous vegetables [28]. A diet low in dietary fibres has been shown to be associated with a high risk of colorectal adenomas [29, 30]. Others have not found any association with dietary components and colorectal adenomas [31, 32].

Case–control studies are not well suited for studies on long-term cause–effect relationships with exposures which change over time and when no secondary exposure data are available for the proper exposure periods. However, the combined existing literature points towards an important dietary causal mechanism, suggesting the possibility of primary prevention of some of the cancers. Should some colorectal cancers develop via adenomas, prevention may also be achieved by removing adenomas when detected in screening programmes or otherwise.

Data in this study stem from the first and second round of the randomised screening trial in Funen, Denmark. From this part of the trial the proportions of Duke's stage A tumours were 52% and Duke's stage B tumours 28%. The proportion of adenomas with villous elements was 15%. More clinical information on this trial has been given previously [8].

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Current and Future Costs of Cancer

Marc A. Koopmanschap, Leona van Roijen, Luc Bonneux and Jan J. Barendregt

Cancer costs in the Netherlands amounted to 4.8% of health care costs in 1988. For five cancer types, and a sixth group covering all other malignancies, costs were broken down by age, sex and disease phase. They showed a remarkably similar pattern of medical consumption. Costs were linked to observed incidence, mortality and estimated prevalence, together allowing for prediction of future costs of cancer. In 2020, as a result of ageing, cancer costs will have increased much more rapidly than total health care costs, in particular for cancer of the lung and prostate. Colorectal cancer costs were predicted for epidemiological scenarios. Our model shows that an increase in future prevalence may bear quite different cost implications. If it is due to higher incidence, the costs will increase substantially. If due to survival improvement, the increase will be less prominent. Simply extrapolating costs based on future prevalence or mortality may produce serious errors.
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INTRODUCTION

AN OPTIMAL allocation of health care resources requires insight into the epidemiology and costs of diseases. Regarding cancer, we need to know both the absolute costs and the relative costs as compared to other diseases and total health care. Furthermore, the impact of demography, changes in medical practice and epidemiology on future health care costs should be analysed.

In this article, we estimate the costs for five cancer categories: cancer of the lung, breast, colorectum, prostate, stomach and all other malignancies in a sixth category. These cancer categories were selected based on their importance for mortality, morbidity and medical consumption.

First, we calculated the total costs per type of cancer, age group and sex for 1988. Next, these costs were assigned to three disease phases: the year following incidence, the year preceding death and the period in between. The estimated costs per patient by disease phase were combined with incidence, mortality and prevalence, as calculated by our cancer disease model. This allows for prediction of future cancer costs for several possible scenarios: a demographic scenario and scenarios concerning expected trends in incidence and survival. The costs predicted by the 'three phase model' were compared with outcomes using simple extrapolations of average costs per patient.

MATERIALS AND METHODS

Total costs of cancer

In a recent study, we estimated total health care costs for the Netherlands in 1988, for the six aforementioned cancer types,

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