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A prospective cohort study on the relationship between onion and leek consumption, garlic supplement use and the risk of colorectal carcinoma in The Netherlands

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The association between onion and leek consumption, garlic supplement use and colon and rectum carcinoma among men and women was evaluated in the Netherlands Cohort Study, a large-scale prospective cohort study on diet and cancer. Onions, leeks, and garlic belong to the *Allium* genus and contain large amounts of potentially chemopreventive compounds. The Netherlands Cohort Study was started in 1986 among 120 852 men and women, aged 55–69 years. Dietary intake was measured with a 150-item food frequency questionnaire. After 3.3 years of follow-up, 150 and 143 incident male and female cases of colon carcinoma, and 93 and 57 cases of rectum carcinoma, respectively, with complete dietary data were available for analysis. Dietary data were available for 1525 men and 1598 women of a randomly selected subcohort, that was followed up to estimate person-time in the entire cohort. In men, the adjusted rate ratios (RRs) in multivariable analysis for colon and rectum carcinoma in the highest compared to the lowest onion consumption categories were 0.87 (95% confidence interval [CI] = 0.48–1.65), and 0.66 (95% CI = 0.28–1.52), respectively. The RRs for proximal colon carcinoma were lower than for distal colon carcinoma. Leek consumption was not associated with colon and rectum carcinoma incidence in men. None of the RRs were significantly different from unity and no trends in the RRs were detected. A lower risk was found for rectum carcinoma in women consuming less than 0.25 onions per day (RR = 0.36, 95% CI = 0.13–0.99), but the trend in the RRs was not statistically significant (P = 0.25). All other RRs for colon and rectum carcinoma associated with onion consumption were slightly higher than one. Leek consumption was not associated with colon and rectum carcinoma incidence. The use of garlic supplements was not associated with colon and rectum carcinoma in men and women combined. This study does not support an inverse association between the consumption of onions and leeks, or the use of garlic supplements and the incidence of male and female colon and rectum carcinoma.

Introduction

Vegetables have long been recognized as important exogenous factors in the aetiology of cancer of colon and rectum. High intake of vegetables might reduce the risk considerably (1). Recent reviews on the role of vegetables and fruit in cancer risk emphasized the strong evidence for a protective effect of vegetable and fruit consumption on risk of colorectal cancer. Certain vegetables, such as cruciferous vegetables and carrots, may be particularly promising in this respect (2–6).

However, in a recently published Australian case–control study on vegetable and fruit consumption and male and female colon cancer, the strongest inverse associations were with onions. In women, all odds ratios in increasing quartiles of consumption were significantly below unity. In men, the inverse risk was stronger for proximal than for distal colon cancer (7).

Onions, but also leeks, garlic, chives and shallots belong to the *Allium* genus. Experimental research suggests an inhibitory role in colon carcinogenesis by certain sulphur containing compounds, such as diallyl sulphide, S-allylmercaptocystein and S-allylcystein, present in *Allium* vegetables (8). Diallyl disulphide, a garlic compound, has recently been shown to reduce the incidence and multiplicity of invasive colon adenocarcinoma in experimental animals (9). Some of the potentially chemopreventive sulphur containing compounds are also present in garlic supplements (10), the most widely used type of dietary supplement by elderly persons in The Netherlands (11). Onions are also important contributors of the flavonol quercetin (12). Flavonols, such as quercetin and kaempferol (present in leeks [13,14]), and the cysteine-containing tripeptide glutathione, which has been detected in onions (15), might act as anticarcinogens as well (16–20).

Results from earlier case-control studies also suggest that high intake of onions or other vegetables belonging to the *Allium* genus may reduce the risk for colon and rectum cancer. In Japan, a decreased risk for colorectal cancer as well as for the subset of cancers in the lower part of the rectum (less than 5 cm from the anus) was observed with high consumption of Japanese leeks. In a preceding study in Hawaii, the risk for colorectal cancer among Hawaiian Japanese was also lower than unity with high consumption of leeks (21,22). High consumption of onions was associated with a significantly reduced risk for colon cancer in a case–control study in the USA (23). In Belgium, both the consumption of leeks and the consumption of onions and/or shallots were inversely associated with the risk for colon cancer and for rectum cancer (24). However, onion and leek consumption were not associated with risk for colorectal cancer in Greece (25). Only in one case–control study, in Japan, higher risks for colon and rectum cancer were observed with onion consumption (26). Garlic consumption was associated with a lower rectum cancer risk in women in China, while no association was found for rectum cancer in men, and also not for male or female colon cancer in this study (27). To date, there has been no report examining associations between *Allium* vegetable consumption and colon and rectum cancer risk in a prospective study.

In 1986, the Netherlands Cohort Study (NLCS*), a large-scale prospective cohort study on diet and cancer, was started among 120 852 men and women (28). We have investigated the relation between onion and leek consumption, the use of garlic supplements and the risk of colon and rectum cancer after 3.3 years of follow-up.

*Abbreviations: NLCS, the Netherlands Cohort Study; RR, rate ratio; CI, confidence interval; OR, odds ratio.

Materials and methods

The Netherlands Cohort Study

A description of the design of the NLCS and the characteristics of the cohort has been published (28). In brief, the NLCS was started in 1986 among 58 279 men and 62 573 women aged 55–69 years, originating from 204 municipalities in The Netherlands with computerized population registries. A self-administered mailed questionnaire was used to collect information on usual diet, lifestyle characteristics, medical history, dietary supplement use and other important risk factors for cancer. Accumulation of person-time in the cohort has been estimated by follow-up of a randomly selected subcohort of 1688 men and 1812 women.

Identification of cases of colon and rectum cancer

Information on cancer incidence has been collected for the entire cohort by record linkage with all nine cancer registries in The Netherlands and with PALGA, the Dutch network and National Database for Pathology. The method of record linkage has been published (29). The present analysis is restricted to cancer incidence in the first 3.3 years of follow-up (from baseline in September 1986 to December 1989). Completeness of follow-up in this period is estimated to be 95% (30).

Study population

After excluding those subjects from the entire group of colon and rectum cancer cases who reported any prevalent cancer other than skin cancer at baseline, and those with incident *in situ* carcinoma, colon and rectum cancer other than carcinoma (sarcoma, lymphoma, unspecified morphology), or without at least a microscopically confirmed diagnosis, 258 incident male and 220 incident female colon and rectum carcinoma cases were available for analysis. Of the subcohort, 1630 men and 1716 women without a previous history of cancer other than skin cancer were included.

Questionnaire

A 150-item semiquantitative food frequency questionnaire was used to collect information on the usual intake of foods and beverages in the year preceding the start of the study. Questionnaire data of all cases and subcohort members have been key-entered twice and processed blinded with respect to case/subcohort status to prevent random and systematic coding errors (31). Two of the questions on vegetable intake specifically focused on the consumption of *Allium* vegetables in the preceding year: 'How many onions did you usually eat per week?' and 'How often have you consumed leek in summer and how often in winter?'. The latter question asked, for each season, to choose from one of six categories ranging from 'never or less than once per month' to '3–7 times per week', including leeks consumed in mixed vegetable dishes. A question on the consumption of other *Allium* vegetables (e.g. garlic, chives) was not included in the baseline questionnaire. The food and beverage part of the questionnaire has been validated against three 3-day diet records (31).

Information on type of dietary supplement, brand name, dose per day, as well as the specific period in which the consumption took place, could be listed in an open-ended question on dietary supplement use. Recall of garlic supplement use was evaluated in a subgroup of the cohort (n = 109) by comparing the questionnaire with information from three personal interviews per person as reference (32).

Data analysis

For the analysis of onion and leek consumption, we used cases and subcohort members with dietary data that were considered as complete (30). Subjects were categorized into four categories of onion consumption (0, < 0.25, 0.25–0.5, and ≥ 0.5 onions per day) and three categories of leek consumption (0, ≤ 2 and > 2 times per month). In the first 3.3 years of follow-up, 150 colon (ICD-O topography code 153.0–9) and 93 rectosigmoid and rectum (ICD-O topography codes 154.0 and 154.1) carcinoma cases with complete dietary data were detected in male cohort members. Of all 150 malignant tumours in the colon, 65 originated in the proximal part (ICD-O topography codes 153.0–1, 153.4–6), 71 in the distal part (ICD-O topography codes 153.2–3 and 153.7), 13 were unspecified (ICD-O topography code 153.9) and one had overlapping boundaries (ICD-O topography code 153.8) (33). Of the 143 female colon carcinoma cases with complete dietary data, 68 had a carcinoma in the proximal and 56 in the distal colon. Fifteen carcinomas were not specified and four had overlapping boundaries. In 57 women, the primary lesion was found in the rectosigmoid junction and rectum.

Analyses of garlic supplement use are based on subjects with complete information on dietary supplement use. Garlic supplement users were defined as those subjects who reported daily use of any garlic supplement for at least one year in the five-year period before baseline. When garlic supplement users also took other dietary supplements in the same period, we separately examined the relation with colon and rectum carcinoma for users of exclusively garlic supplements with nonusers of dietary supplements as reference, and for those consuming garlic together with other supplements. For this analysis, subjects taking any other supplement were used as reference.

To determine whether onion and leek consumption, or the use of garlic supplements was associated with other potential risk factors for colon and rectum cancer, we compared for male and female subcohort members, the mean age, Quetelet index, alcohol intake, and dietary intake of vitamin C or β-carotene between the categories of consumption. The dietary intake of vitamin C and β-carotene was computed by using the Dutch food composition table (34). The proportions of nonsmokers, subjects with a personal history of chronic intestinal disease or cholecystectomy, or with a family history of intestinal cancer and the proportion of nulliparous women (for female subcohort members) were also compared between the exposure categories.

Case-cohort analyses were performed based on the assumption that survival times were exponentially distributed in this follow-up period (30). In age-adjusted stratified analyses, we computed Mantel–Haenszel rate ratios and 95% confidence intervals for each category of onion and leek consumption and for garlic supplement use, and tests for trend in the rate ratios. In the multivariable analyses, we further adjusted for other covariables.

All 95% confidence intervals were corrected for the additional variance introduced by using a subcohort instead of the complete cohort. Tests for trend in the rate ratios were based on likelihood ratio tests. Separate analyses were conducted for male and female colon and rectum carcinoma. Since there is evidence of subsite-specific differences in colon cancer risk associated with vegetable consumption (7,35), we also evaluated whether the role of onion and leek consumption differs or varies for proximal and distal colon cancer. To evaluate a potential influence of preclinical symptoms of large intestinal cancer on dietary habits, analyses were also performed for cases diagnosed after the first year of follow-up.

Results

In Table I, we present the distributions of onion and leek consumption and garlic supplement use in cases and subcohort. Male colon carcinoma cases consumed not as many onions as male subcohort members. The proportions of male rectum carcinoma cases, however, were both in the lowest as well as in the highest category of onion consumption smaller than in the subcohort. The proportions of the subjects consuming leeks more than twice per month were larger among male colon carcinoma cases and smaller among male rectum carcinoma cases than among subcohort members. The proportions of users of exclusively garlic supplements were larger in the two case groups, while only a small proportion of the male colon carcinoma cases took garlic supplements together with any other supplement.

In women, the proportions of cases in the lowest as well as in the highest onion consumption categories were larger than in the subcohort. The proportions of subjects in the highest leek consumption category were larger among female colon carcinoma cases and smaller among female rectum carcinoma cases than among female subcohort members. The proportions of users of garlic supplements without any other supplement were smaller among female cases than among subcohort members.

Baseline characteristics of the population are presented in Table II. Compared with male subcohort members, male colon and rectum cancer cases were older at baseline. A higher percentage of male cases were ex-smokers, had a history of cholecystectomy or a family history of intestinal cancer. A higher proportion of subjects with chronic intestinal disease (e.g. Crohn's disease, colitis ulcerosa) was seen in male colon carcinoma cases, and a lower proportion in rectum carcinoma cases. The distributions of educational level were nearly equal in cases and subcohort.

Female colon and rectum carcinoma cases were older than subcohort members. Furthermore, higher percentages of cases had a history of chronic intestinal disease or cholecystectomy. The percentage of female subjects with a family history of intestinal cancer was nearly twice as high in colon carcinoma

Table I. Onion and leek consumption and garlic supplement use among male and female colon and rectum carcinoma cases and among subcohort members[a]

Allium consumption	Men			Women		
	Colon (%) (n = 150)	Rectum (%) (n = 93)	Subcohort (%) (n = 1525)	Colon (%) (n = 143)	Rectum (%) (n = 57)	Subcohort (%) (n = 1598)
Onions (number/day)						
0	22.7	19.4	20.5	23.1	28.1	20.8
< 0.25	31.3	34.4	31.0	28.0	14.0	28.0
0.25–0.50	32.0	34.4	32.6	32.2	40.4	37.6
≥ 0.50	14.0	11.8	15.9	16.8	17.5	13.5
Leeks (freq/month)						
0	34.7	35.5	31.9	32.2	29.8	29.3
≤ 2	34.0	41.9	39.9	33.6	38.6	37.7
> 2	31.3	22.6	28.2	34.3	31.6	32.9
Garlic supplement use[b]						
No supplement	74.4	82.8	77.9	57.8	67.7	64.5
Exclusively garlic	6.4	7.1	4.1	3.9	3.1	5.0
Garlic + any other	1.9	0	3.2	7.8	4.6	5.1
Any other	17.3	10.1	14.8	30.5	24.6	25.3

[a]Percentages are presented for the total population available for analysis as described in the methods section.
[b]The categories of garlic supplement use are mutually exclusive.

Table II. Distribution (%) of male and female colon and rectum carcinoma cases and subcohort members with complete dietary data, by selected baseline characteristics

Characteristics	Men			Women		
	Colon (n = 150)	Rectum (n = 93)	Subcohort (n = 1525)	Colon (n = 143)	Rectum (n = 57)	Subcohort (n = 1598)
Age (years)						
55–59	24.7	25.8	38.2	27.3	21.1	38.5
60–64	40.7	45.2	35.0	36.4	38.6	34.3
65–69	34.7	29.0	26.8	36.4	40.0	27.2
Smoking status						
Never	8.0	8.6	9.6	58.0	63.2	59.0
Ex-smoker	56.0	58.1	48.4	23 1	15.8	20.2
Current smoker	36.0	33.3	42.0	18.9	21.1	20.8
Previous history of chronic intestinal disease	4.0	2.2	3.1	7.0	5.3	4.6
Cholecystectomy	9.3	7.5	5.4	21.0	19.3	14.6
Intestinal cancer in family	6.7	9.7	5.3	9.1	5.3	5.4
Highest educational level						
Primary school	22.8	25.8	25.9	33.8	28.1	34.0
Lower vocational	20.8	19.4	21.2	21.1	31.6	22.8
Second/ medium vocational	36.2	36.7	35.0	33.8	29.8	34.7
University/ higher vocational	20.1	17.2	17.9	11.3	10.5	8.5
Parity						
0				20.4	15.8	17.5
1				9.9	12.3	8.2
2				26.8	28.1	22.0
> 2				43.0	43.9	52.3

cases as in the subcohort, whereas the percentages in rectum carcinoma cases and subcohort were nearly equal. The distributions of female cases according to smoking status, educational level and parity were somewhat different from those in the subcohort.

Associations between onion and leek consumption and potential confounders are presented in Table III, for male and female subcohort members in the lowest and highest consumption categories. Associations between garlic supplements use and other risk factors are presented for those not using dietary supplements and for those using garlic supplements with or without any other supplement. In men, the mean ages were slightly higher in the lowest onion and leek consumption categories than in the highest categories. No differences in the mean Quetelet index were observed, whereas the mean alcohol intake was lowest in the lowest consumption categories and the mean vitamin C and β-carotene intakes highest in the highest consumption categories. Both in the lowest onion and leek consumption categories, a higher proportion of nonsmokers and subjects with a history of chronic intestinal disease or cholecystectomy was observed. The proportion of male subcohort members with a family history of intestinal cancer was higher in those not consuming onions, and lower in those not eating leeks. The mean age, Quetelet index and alcohol intake were nearly identical in male garlic supplement users and nonusers of dietary supplements. Com-

Table III. Associations between onion and leek consumption, garlic supplement use and potential confounders in male and female subcohort members

Characteristics	Onion consumption (number/day)[a]		Leek consumption (freq/month)[a]		Garlic supplement use	
	0	≥0.5	0	>2	No suppl.	Yes[b]
Men						
Age (mean, years)	61.5	61.1	61.6	61.4	61 2	62.3
Quetelet index (mean, kg/m^2)	25.1	25.3	25.1	25.0	25.1	5.2
Alcohol (mean, g/day)	11.7	20.3	13.6	15.7	14.1	14.2
Vitamin C (mean, mg/day)	85.6	116.9	93.3	106.9	89.4	112.1
β-carotene (mean, mg Eq vit A)	0.36	0.51	0.37	0.41	0.30	0.42
Never smoking (%)	13.4	9.1	9.1	7.9	9.5	10.2
Chron. intest. disease (%)	6.1	2.1	4.7	2.6	2.4	1.7
Cholecystectomy (%)	5.4	2.9	4.9	3.5	5.6	3.4
Intest. cancer in family (%)	6.7	4.5	5.1	6.0	5.0	6.8
Women						
Age (mean, years)	61.9	61.4	61.8	61.1	61.5	61.5
Quetelet Index (mean, kg/m^2)	25.2	25.1	25.3	25.2	25.4	25.7
Alcohol (mean, g/day)	4.3	8.4	4.8	6.4	5.4	5.5
Vitamin C (mean, mg/day)	100.7	123.8	99.7	119.2	96.1	112 9
β-carotene (mean, mg Eq vit A)	0.38	0.51	0.37	0.50	0.30	0.41
Never smoking (%)	65.2	52.3	60.6	59.9	61.4	58.6
Chron. intest. disease (%)	7.5	3.2	5.5	3.8	3.3	3.4
Cholecystectomy (%)	13.2	12.5	14.3	12 7	12.9	15.5
Intest. cancer in family (%)	5.1	6.5	4.3	5.5	5.3	4.6
Nulliparous (%)	20.2	18.8	19.1	17.8	16.6	11.7

[a]The proportions and means are shown for the lowest and highest consumption categories.
[b]Users of garlic supplements with or without any other dietary supplement.

pared with nonusers of dietary supplements, higher mean intakes of vitamin C and β-carotene, higher proportions of nonsmokers and subjects with a family history of intestinal cancer, and lower proportions of those with a history of chronic intestinal disease or cholecystectomy, were found in male garlic supplement users.

In women, a higher mean age and a lower mean alcohol intake were seen in the lowest onion and leek consumption category. The mean vitamin C and β-carotene intakes were higher in highest consumption categories. A higher percentage of nonsmokers, women with a history of chronic intestinal disease or cholecystectomy, or without children was seen in lowest consumption categories. The percentages of women with a family history of intestinal cancer were lower in the lowest consumption categories. In female garlic supplement users a higher mean Quetelet index, mean vitamin C and β-carotene intake, and percentage of women with a history of cholecystectomy was seen, compared with nonusers of dietary supplements, and a lower proportion of nonsmokers, female subcohort members with a family history of intestinal cancer, or without children.

Table IV presents rate ratios (RR) and 95% confidence intervals (CI) of male colon and rectum carcinoma associated with onion and leek consumption, controlled for age in stratified analysis and further controlled for other variables in multivariable analysis.

A decreasing colon carcinoma risk was observed with increasing onion consumption. The RR in the highest onion intake category was 0.87 (95% CI = 0.48–1.65). RRs for carcinoma in the proximal colon were lower than for carcinoma in the entire colon, except for the RR in the highest consumption category. All RRs for distal colon carcinoma were higher than one, but none of them significantly. The RR for rectum carcinoma associated with onion consumption was lower than one in the highest category (RR = 0.66, 95% CI = 0.28–1.52). None of the RRs for colon carcinoma associated with leek consumption were significantly different from unity. The RRs for rectum carcinoma were lower in higher leek consumption categories. None of the RRs for rectum carcinoma with each consumption category and none of the tests for trend were statistically significant.

In women, the Mantel–Haenszel RR for colon carcinoma was higher than one in the highest onion consumption category (Table V). When all other risk factors were included in the model, the RR increased to 1.49 (95% CI = 0.79–2.81). The highest RRs were found for carcinoma in the distal colon (RR = 1.78, 95% CI = 0.68–4.64 in the highest onion consumption category). The RR for rectum carcinoma associated with onion consumption was higher than one in the highest intake category, but lower than one in the category '<0.25 onions per day' (RR = 0.36, 95% CI = 0.13–0.99). Leek consumption was not associated with female colon or rectum carcinoma. None of the RRs were significantly different from unity and none of the tests for trend were statistically significant.

All analyses have also been carried out for those cases diagnosed after the first year of follow-up. All RRs were nearly similar to those found for the entire case group. None of the RRs and tests for trend were statistically significant (results not shown).

The RRs for colon and rectum carcinoma associated with garlic supplement use are presented for men and women together, since the RRs for men and women were nearly similar (Table VI). Garlic supplement use was associated with a higher colon carcinoma risk when compared to not using dietary supplements, but not significantly (RR = 1.26, 95% CI = 0.84–1.91). When cases using other dietary supplements were excluded, the RR of colon carcinoma increased to 1.36 (95% CI = 0.79–2.35). We observed a slightly lower risk for colon carcinoma with the use of garlic supplements together

Table IV. Rate ratios and 95% confidence intervals of male colon and rectum carcinoma according to onion and leek consumption, in stratified[a] and multivariable[b] analysis

	Onion consumption (number/day)				Leek consumption (freq/month)		
	0	<0.25	<0.5	≥0.5	0	≤2	>2
Colon							
PY in subcohort[c]	1007	1521	1597	768	1568	1946	1379
No. of cases	34	47	48	21	52	51	47
RR_{MH} (95% CI)[a]	1.00[+]	0.92 (0.58–1.46)	0.89 (0.56–1.41)	0.81 (0.46–1.43)	1.00[+]	0.79 (0.53–1.18)	1.03 (0.68–1.56)
RR (95% CI)[b]	1.00[+]	1.01 (0.62–1.64)	0.97 (0.59–1.59)	0.87 (0.48–1.65)	1.00[+]	0.77 (0.50–1.17)	1.10 (0.71–1.70)
	Trend test $\chi^2 = 0.53$ ($P = 0.47$)				Trend test $\chi^2 = 0.006$ ($P = 0.94$)		
Proximal colon							
No. of cases	17	22	17	9	20	24	21
RR_{MH} (95% CI)[a]	1.00[+]	0.88 (0.46–1.68)	0.63 (0.32–1.26)	0.86 (0.40–1.85)	1.00[+]	0.98 (0.54–1.78)	1.18 (0.63–2.20)
RR (95% CI)[b]	1.00[+]	0.97 (0.49–1.93)	0.67 (0.31–1.43)	0.93 (0.39–2.23)	1.00[+]	0.88 (0.46–1.66)	1.32 (0.67–2.54)
	Trend test $\chi^2 = 0.43$ ($P = 0.51$)				Trend test $\chi^2 = 0.70$ ($P = 0.40$)		
Distal colon							
No. of cases	13	21	26	11	25	24	22
RR_{MH} (95% CI)[a]	1.00[+]	1.12 (0.55–2.26)	1.23 (0.62–2.44)	1.16 (0.51–2.64)	1.00[+]	0.80 (0.45–1.41)	0.97 (0.54–1.73)
RR (95% CI)[b]	1.00[+]	1.29 (0.61–2.71)	1.48 (0.71–3.09)	1.47 (0.61–3.53)	1.00[+]	0.84 (0.47–1.50)	0.97 (0.52–1.82)
	Trend test $\chi^2 = 1.07$ ($P = 0.30$)				Trend test $\chi^2 = 0.02$ ($P = 0.89$)		
Rectum							
PY in subcohort	1007	1522	1595	772	1570	1946	1379
No. of cases	18	32	32	11	33	39	21
RR_{MH} (95% CI)[a]	1.00[+]	1.19 (0.65–2.17)	1.11 (0.61–2.01)	0.81 (0.37–1.77)	1.00[+]	0.97 (0.60–1.57)	0.73 (0.42–1.29)
RR (95% CI)[b]	1.00[+]	1.12 (0.61–2.08)	0.99 (0.53–1.85)	0.66 (0.28–1.52)	1.00[+]	0.99 (0.60–1.63)	0.72 (0.40–1.30)
	Trend test $\chi^2 = 0.90$ ($P = 0.34$)				Trend test $\chi^2 = 1.18$ ($P = 0.28$)		

[a]Stratified by age in three categories: 55–59, 60–64, 65–69 years.
[b]Adjusted for age, Quetelet index, alcohol intake, vitamin C and β-carotene as continuous variables, and smoking status, education, family history of large intestinal cancer, history of cholecystectomy and chronic intestinal disease as categorical variables.
[c]PY: Person-years in the subcohort.
[+]Reference category.

Table V. Rate ratios and 95% confidence intervals of female colon and rectum carcinoma according to onion and leek consumption, in stratified[a] and multivariable[b] analysis

	Onion consumption (number/day)				Leek consumption (freq/month)		
	0	<0.25	<0.5	≥0.5	0	≤2	>2
Colon							
PY in subcohort[c]	1081	1456	1960	698	1521	1958	1715
No. of cases	33	40	46	24	46	48	49
RR_{MH} (95% CI)[a]	1.00[+]	0.91 (0.56–1.49)	0.81 (0.50–1.31)	1.13 (0.65–1.97)	1.00[+]	0.82 (0.54–1.25)	0.99 (0.65–1.52)
RR (95% CI)[b]	1.00[+]	1.21 (0.70–2.09)	1.11 (0.65–1.90)	1.49 (0.79–2.81)	1.00[+]	0.91 (0.57–1.45)	1.18 (0.73–1.89)
	Trend test $\chi^2 = 0.97$ ($P = 0.32$)				Trend test $\chi^2 = 0.55$ ($P = 0.46$)		
Proximal colon							
No. of cases	16	19	20	13	22	20	26
RR_{MH} (95% CI)[a]	1.00[+]	0.83 (0.42–1.65)	0.72 (0.36–1.41)	1.19 (0.56–2.51)	1.00[+]	0.65 (0.36–1.19)	1.02 (0.57–1.80)
RR (95% CI)[b]	1.00[+]	1.09 (0.50–2.36)	1.05 (0.49–2.23)	1.50 (0.62–3.60)	1.00[+]	0.77 (0.39–1.53)	1.28 (0.67–2.46)
	Trend test $\chi^2 = 0.54$ ($P = 0.46$)				Trend test $\chi^2 = 0.70$ ($P = 0.40$)		
Distal colon							
No. of cases	10	15	21	10	15	25	16
RR_{MH} (95% CI)[a]	1.00[+]	1.02 (0.47–2.21)	1.07 (0.52–2.20)	1.31 (0.56–3.08)	1.00[+]	1.33 (0.71–2.50)	0.99 (0.50–1.97)
RR (95% CI)[b]	1.00[+]	1.21 (0.51–2.84)	1.27 (0.56–2.91)	1.78 (0.68–4.64)	1.00[+]	1.25 (0.63–2.46)	0.98 (0.46–2.10)
	Trend test $\chi^2 = 1.29$ ($P = 0.26$)				Trend test $\chi^2 = 0.002$ ($P = 0.96$)		
Rectum							
PY in subcohort	1083	1457	1960	698	1525	1957	1716
No. of cases	16	8	23	10	17	22	18
RR_{MH} (95% CI)[a]	1.00[+]	0.39 (0.16–0.94)	0.87 (0.45–1.68)	1.00 (0.44–2.25)	1.00[+]	1.03 (0.54–1.96)	0.99 (0.50–1.98)
RR (95% CI)[b]	1.00[+]	0.36 (0.13–0.99)	1.00 (0.47–2.12)	1.34 (0.55–3.31)	1.00[+]	1.18 (0.56–2.50)	1.31 (0.60–2.85)
	Trend test $\chi^2 = 1.32$ ($P = 0.25$)				Trend test $\chi^2 = 0.49$ ($P = 0.49$)		

[a]Stratified by age in three categories: 55–59, 60–64, 65–69 years.
[b]Adjusted for age, Quetelet index, alcohol intake, vitamin C and β-carotene as continuous variables, and smoking status, education, family history of large intestinal cancer, history of cholecystectomy and chronic intestinal disease as categorical variables.
[c]PY: Person-years in the subcohort.
[+]Reference category.

with other supplements: RR = 0.93 (95% CI = 0.51–1.71). The RR for rectum carcinoma associated with use of garlic supplements was lower than one (RR = 0.77, 95% CI = 0.41–1.46), but when users of other supplements than garlic were excluded the RR was higher than one (RR = 1.28, 95% CI = 0.63–2.60). None of the RRs were significantly different

Table VI. Rate ratios and 95% confidence intervals of colon and rectum carcinoma according to garlic supplement use, in stratified[a] and multivariable[b] analysis

	Garlic vs. no supplement			Garlic vs. any other supplement	
	No	Garlic supplements	Exclusively garlic	Any other[d]	Garlic + any other[e]
Colon					
PY in subcohort[c]	7270	937	488	2178	449
No. of cases	205	31	16	94	15
RR_{MH} (95% CI)[a]	1.00[+]	1.21 (0.81–1.80)	1.20 (0.70–2.05)	1.00[+]	0.93 (0.53–1.63)
RR (95% CI)[b]	1.00[+]	1.26 (0.84–1.91)	1.36 (0.79–2.35)	1.00[+]	0.93 (0.51–1.71)
Rectum					
PY in subcohort[c]	7672	565	490	1406	283
No. of cases	126	12	9	16	3
RR_{MH} (95% CI)[a]	1.00[+]	0.80 (0.43–1.47)	1.16 (0.57–2.34)		
RR (95% CI)[b]	1.00[+]	0.77 (0.41–1.46)	1.28 (0.63–2.60)		

[a]Stratified by gender and age in three categories: 55–59, 60–64 and 65–69 years.
[b]Adjusted for age, vitamin C and β-carotene as continuous variables, and gender, smoking status, education, family history of intestinal cancer, previous history of chronic intestinal disease or cholecystectomy as categorical variables.
[c]PY: Person-years in the subcohort.
[d]The distributions of 'any other dietary supplements', mentioned by colon carcinoma cases and subcohort members, were: vitamin AD 11.7% and 8.7%; vitamin B 26.2% and 22.2%; vitamin C 17.5% and 18.2%; vitamin E 5.8% and 5.2%; multivitamins/minerals 8.8 and 13.6%; calcium 7.8% and 9.6%; brewers' yeast 4.9% and 7.5%.
[e]Other supplements used together with garlic supplements by colon carcinoma cases and subcohort members, were: vitamin AD 4.5% and 4.2%; vitamin B 11.4% and 8.9%; vitamin C 4.5% and 9.4%; vitamin E 2.3% and 3.0%; multivitamins/minerals 2.3% and 6.4%; calcium 11.4% and 6.1%; brewers' yeast 9.8% and 8.3%.
[+]Reference category.

from unity. The number of rectum carcinoma cases using garlic supplements together with other supplements was too low to provide meaningful estimates.

Discussion

In the Netherlands Cohort Study, we have found no evidence of an inverse association between the consumption of onions and leeks, the use of garlic supplements, and the incidence of colon and rectum carcinoma in men and women. We also found no evidence for a lower risk of carcinoma in the proximal and distal part of the colon, or for cases diagnosed after the first year of follow-up.

Our results do not support the findings from a number of case-control studies of *Allium* vegetable consumption and colon and rectum cancer risk.

Of the eight case–control studies that investigated the association with *Allium* vegetables as individual food group, six reported an inverse association with colon and rectum cancer (7,21–25). In the most recently published case–control study, by Steinmetz and Potter, the consumption of onions was associated with the lowest colon adenocarcinoma risk of all vegetable groups. In women, all odds ratios (OR) in increasing quartiles of consumption were significantly below unit (1.00, 0.39, 0.38, 0.42, after controlling for protein intake, age at first live birth, Quetelet index and alcohol intake). In men, a stronger inverse association was observed for proximal colon (protein-adjusted OR = 0.23, with 95% CI = 0.07–0.83 in the highest quartile of consumption), than for distal colon cancer (7). One study reported no association between onion and leek consumption and colorectal cancer (25), and one showed a positive association between onion consumption and colon and rectum cancer (26). However, this higher risk may have been caused by the selection of hospital patients with severe gastric and intestinal disorders as controls. Patients suffering from gastric complaints may have avoided the consumption of *Allium* vegetables. In the other studies that used hospital controls, patients with orthopaedic diseases (25) or any other diseases except gastrointestinal disorders (21,22,27) were selected. In the case–control studies by Tuyns *et al.* (24) and Steinmetz and Potter (7) population controls were selected, while Graham *et al.* selected neighbourhood controls (23).

A potential problem in prospective cohort studies is the possibility of selection bias if there is exposure-related loss to follow-up (36). In the NLCS, however, selection bias is unlikely since the completeness of follow-up of cancer incidence was estimated at 95% (30).

One of the potential limitations of our study is that we are not entirely sure that the absence of a relation between onion and leek consumption and colon and rectum carcinoma risk has not been caused by nondifferential misclassification of exposure. Although the validity of the semiquantitative food frequency questionnaire has been assessed for food groups, information on its validity regarding onion and leek consumption is not available (31). Recall of garlic supplement use was 77.8%, which may provide enough precision to classify individuals into distinctive categories of intake (32).

Unfortunately, we did not enquire after the consumption of other *Allium* vegetables, such as fresh garlic, in the baseline questionnaire. However, in a later version of the questionnaire that was completed by members of the subcohort in 1990, only 1.8% of the men and 1.4% of the women reported daily consumption of fresh garlic. The proportions of garlic supplement users at baseline were much higher: 7.3% of the male and 10.1% female subcohort members took at least one garlic supplement per day.

We included many other, nondietary as well as dietary, determinants of colon and rectum carcinoma as potential confounders in the multivariable models. However, it might still be possible that another factor than we controlled for in our analysis, might be involved. Regarding the published studies, only in the study by Steinmetz and Potter (7), adjustment was made for other variables than age, gender or place of residence.

Another reason for finding no association between onion and leek consumption, garlic supplement use and incidence of colon and rectum carcinoma in our study, could be that the contrasts between the highest and lowest consumption categories within our study population, or the level of intake of potentially anticarcinogenic compounds from Allium vegetables, are not high enough to detect an association.

We have categorized intake of onions based on the number of onions usually consumed, without taking size or weight into account. However, this is only relevant when onions vary greatly in size, which is not the case in The Netherlands (37). Furthermore, the amount of potentially anticarcinogenic compounds in Allium vegetables not only depends on size but also on variety, growing conditions, and storage and preparation methods (38–40). We did not inquire into such detail in our questionnaire.

However, since in some of the case–control studies contrasts between the comparison groups were simply yes/no (24,27), high/low (21,22), or not specified (23,25), it is not clear whether the consumption levels differ between the study populations. In two studies, cases and controls were categorized in quantiles, with low frequency of consumption as reference category (7,26).

In contrast with retrospective case-control studies, prospective cohort studies are considered not to be biased by differential recall of past dietary intake due to awareness of the disease status (36). However, it is not very likely that this type of recall bias is accountable for the difference between results from case-control studies and our prospective cohort study, since differential recall of Allium vegetable intake by cases and controls leads to the observed inverse associations only if cases recall their consumption not as frequently or accurately as controls. Nevertheless, cases and controls might have recalled their past dietary intake differently, when their recall was influenced by current dietary habits (41).

Also, the difficulty to measure exposure in the etiologically relevant period is a plausible explanation. Dietary habits might have been changed due to physical symptoms prior to the diagnosis of cancer. Only in the study by Steinmetz and Potter, the investigators tried to eliminate a potential influence of disease symptoms on dietary intake. Subjects were asked to report their diet 12 months before the interview, if they had made recent dietary changes (in 26% of the cases and 13% of the controls) (7). Although in some of the other case-control studies the investigators specifically asked information on dietary habits before the onset of disease (24,25,27), it is not clear whether the cases were able to remember the exact time of onset of symptoms associated with the disease. In the study by Tajima and Tominaga, dietary habits one or two years before visiting the hospital were asked, disregarding the time between interview and the diagnosis of cancer (26). Haenszel *et al.*(21) did not specify the time reference, and Graham *et al.*(23) measured current diet. In the NLCS, we have examined the possibility of an effect of preclinical physical symptoms on dietary habits by excluding cases diagnosed in the first year of follow-up. The RRs were practically similar to those observed for the entire follow-up period. However, whether a one-year period is long enough can only be investigated when a longer follow-up period is completed.

In conclusion, we found no evidence of an association between onion and leek consumption, the use of garlic supplements and the incidence of male and female colon and rectum carcinoma.

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