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A Prospective Cohort Study on Vegetable and Fruit Consumption and Stomach Cancer Risk in the Netherlands

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The association between vegetable and fruit consumption and stomach cancer risk was investigated in the Netherlands Cohort Study among 120,852 men and women aged 55–69 years at the start in September 1986. Analyses were based on 282 incident stomach cancer cases after 6.3 years of follow-up. Age- and sex-adjusted rate ratios of stomach cancer in increasing quintiles of combined vegetable and fruit consumption were 1.00, 0.70, 0.65, 0.76, and 0.64 (p trend = 0.04). Multivariate analysis resulted in rate ratios that were somewhat closer to one (p trend = 0.14). Furthermore, inverse associations for total vegetables, pulses, raw leafy vegetables, total fruit, citrus fruit, and apples and pears that were observed in crude analyses became weaker or disappeared in multivariate analyses. Total vegetable, but not fruit, consumption was significantly lower in cases diagnosed in the first follow-up year. In analyses limited to first year cases (resembling a case-control study), rate ratios for increasing tertiles of total vegetable consumption were 1.00, 0.17, and 0.18 (p trend = 0.0001), which may indicate the presence of information bias in case-control studies. This prospective study suggests that vegetable and fruit consumption was not clearly associated with stomach cancer risk in the Dutch population. The findings of this study are comparable with findings of other cohort studies, but they do not support the findings of case-control studies. *Am J Epidemiol* 1998;148:842–53.

cohort studies; fruit; questionnaires; stomach neoplasms; vegetables

In recent reviews of the epidemiologic literature, it was concluded that a high consumption of vegetables and fruit is rather strongly and consistently associated with a reduced stomach cancer risk (1–3). Persons with a high intake compared with a low intake on average tended to have a 50 percent reduction in stomach cancer risk (4). However, this epidemiologic evidence is mainly based on studies with a case-control design that may be hampered by information bias. The results of the few prospective studies that have been conducted so far were less consistent (5–11). The associations with stomach cancer risk, if any, tended to be less strong than the ones reported in case-control studies. Generally, information on the consumption of vegetables and fruit in the prospective studies was not very detailed, and adjustment for confounding was poor. In addition, none of these studies assessed the independent effect of specific types of vegetables or fruit by adjusting for total vegetables or fruit. The prospective studies were conducted in both Western and non-Western populations, that is, Japanese, Chinese, American men of Scandinavian and German descent, and American women. These populations were almost all at relatively high risk for stomach cancer. Here, we report results of the association between various types of vegetables and fruit and stomach cancer risk in a large-scale prospective cohort study in the Netherlands (a relatively low risk population) after 6.3 years of follow-up.

MATERIALS AND METHODS

The cohort study

The Netherlands Cohort Study on diet and cancer is a prospective cohort study that started in September 1986 among the general population. A detailed description of the study design has been reported elsewhere (12). Briefly, the cohort included 62,573 women and 58,279 men aged 55–69 years at the beginning of the study. At baseline, the cohort members completed a mailed, self-administered questionnaire on dietary habits, smoking, occupation, medical history, personal and family history of cancer, and demographic data. For data analysis, the case-cohort approach was used in which cases are derived from the entire cohort, while the person-years at risk of the entire cohort are estimated from a random sample of 3,500 subjects (subcohort) (13). This subcohort (1,688

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men, 1,812 women) has been followed up biennially for vital status information in order to estimate the accumulated person time in the cohort. No subcohort members were lost to follow-up. Follow-up for incident cancer has been established by record linkage with cancer registries and a pathology register (14). The present analysis is restricted to cancer incidence in the first 6.3 years of follow-up from September 1986 until December 1992. After the exclusion of subjects reporting prevalent stomach cancer at baseline, cases with in situ stomach carcinoma, and cases with stomach cancer other than carcinoma or without microscopically confirmed stomach cancer, there were 310 (242 men, 68 women) incident stomach carcinoma cases remaining. In the subcohort, 1,630 men and 1,716 women remained after the exclusion of prevalent cancer cases other than skin cancer. In the subcohort, eight stomach cancer cases were detected.

The dietary questionnaire

The dietary section of the questionnaire was a 150-item semiquantitative food frequency questionnaire concentrating on the usual consumption of food and beverages during the year preceding the start of the study. The questionnaire was validated against a 9-day diet record (15). The Spearman correlation coefficients between the dietary record and the questionnaire were 0.38 and 0.60 for total vegetable and total fruit consumption, respectively (15). Regarding vegetable consumption, participants were asked to report their consumption frequency of 12 prepared and five raw vegetables, separately for summer and winter. They could choose one of six categories, ranging from "never or less than once per month" to "3–7 times per week." Portion sizes were asked for string/French beans and prepared endive. As for tomatoes and onions, participants were asked how many pieces they usually ate per week; for sweet peppers, per month; and for mushrooms, how many 250-g boxes per month. For tomatoes and sweet peppers, these questions were asked for summer and winter specifically. For fruit, participants were asked to report their consumption frequency of eight different types of fruit and the number of pieces they ate each time. For fruit juices, the frequency of consumption and the number of glasses were asked. The seven frequency categories ranged from "never or less than once per month" to "6–7 times per week." Finally, participants could mention other types of fruit used once a week or more in an open-ended question.

Data analysis

Subjects with incomplete or inconsistent dietary data were excluded, leaving 282 stomach cancer cases and 3,123 subcohort members for fruit analyses (15). In order to check the consistency of the responses on vegetable questions, we computed a vegetable error index for each subject based on a count of inconsistencies. If a score of a subject exceeded a preset value, i.e., more than three errors, the subject was excluded, leaving 265 stomach cancer cases and 2,953 subcohort members for vegetable analyses.

The variables of major interest were the intake of total vegetables and fruit combined, total vegetables, total fruit, several vegetable and fruit groups, and specific types of vegetables and fruit (see table 1). The *Allium* vegetables onion and leek were not included in the analyses because they have been examined in the Netherlands Cohort Study previously (16).

For vegetables, cases and subcohort members were categorized according to a combined summer and winter consumption frequency. Because individual portion sizes of prepared vegetables were correlated in the pilot study data, the individual portion sizes of string/French beans and prepared endive were used to derive the individual portion size of other prepared vegetables for each person. The mean daily vegetable consumption (g/day) was calculated by multiplying frequency and portion size. For the calculation of mean daily fruit consumption (g/day), frequency and standard weights were used. The intake values of vegetables and fruit were categorized into quintiles, tertiles, or categories, depending on the distribution in the subcohort.

Analyses were conducted for men and women together. Age, sex, level of education (17), stomach disorders, family history of stomach cancer, smoking status, fruit consumption (in the case of vegetable analyses), and vegetable consumption (in the case of fruit analyses) were considered as potential confounders. Participants who reported having an ulcer, a stomach bleeding, or a stomach operation because of bleeding in the past and/or reported having previously taken medication for stomach complaints longer than half a year were defined as having stomach disorders. On average, they reported having the first complaints 20 years ago before baseline. Nitrate and nitrite consumption and energy intake were not included in multivariate analyses, because they were not associated with stomach cancer risk in our study (18). Furthermore, inclusion of these three factors in the model did not change the risk estimates. The GLIM statistical package was used to compute rate ratios of stomach cancer and their 95 percent confidence intervals (19). Exponentially distributed survival times were assumed in the follow-up period. Specific macros were developed to account for the additional variance introduced by using the subcohort instead of the entire cohort (20).

Tests for trend in the rate ratios were based on likelihood ratio tests. Two-sided p values were used throughout this article.

For each category of vegetable and fruit consumption combined, total vegetables, total fruit, and vegetable and fruit groups, both age- and sex-adjusted rate ratios and multivariate rate ratios were computed. Furthermore, multivariate rate ratios for continuous estimates of total vegetables and fruit and specific vegetables and fruit were calculated per increment of 25 g/day. The independent contribution of specific vegetables and fruit was assessed by analyses in which total vegetable or fruit consumption was included in the model, respectively. To evaluate the potential influence of vegetable and fruit consumption on prediagnostic symptoms of stomach cancer, we first calculated the mean intake of vegetable and fruit consumption combined, of total vegetables, and of fruit for cases grouped according to the year of follow-up. Thereafter, analyses were conducted after excluding cases diagnosed in the first year of follow-up and analyses limited to cases diagnosed in the first year of follow-up for vegetable and fruit consumption combined (21). Furthermore, analyses for vegetable and fruit consumption combined were conducted for subjects with and without stomach disorders to evaluate whether results are different because of changes in dietary habits related to stomach disorders.

RESULTS

Differences in the mean daily vegetable consumption between men and women in the subcohort were small (table 1). Women in the subcohort consumed more fruit than did men (196.1 vs. 154.9 g/day), which was due to a difference in consumption of nearly all types of fruit and fruit juices. Cases consumed less vegetables than did subcohort members. This was true for men and especially for women. Both male and female cases also consumed less fruit and fruit juices than did subcohort members, except that female cases consumed more citrus fruit than did female subcohort members.

Fruit consumption in the subcohort was positively associated with age ($p < 0.01$) (table 2). Current smokers and subjects with stomach complaints consumed less vegetables and fruit than did exsmokers, nonsmokers, and subjects without stomach disorders. Both vegetable and fruit consumption differed between subjects with a different level of education. Neither vegetable nor fruit consumption differed between subjects with and without stomach cancer in the family. As expected, a positive association existed between vegetable and fruit consumption ($p < 0.001$).

Table 3 shows categorical analyses of vegetable and fruit consumption. For vegetable and fruit consumption combined, a significant inverse association with stomach cancer risk was observed in the age- and sex-adjusted analysis (trend $p = 0.04$), with rate ratios of 0.70, 0.65, 0.76, and 0.64 for the second to fifth quintiles. After multivariate adjustment, the test for trend was not longer statistically significant. After adjustment for age and sex, a nonsignificant inverse association between total vegetables and stomach cancer was shown. The rate ratios for increasing quintiles were 1.00, 0.76, 0.47, 0.64, and 0.79 (trend $p = 0.10$). This *U*-shaped association was also found for prepared vegetables and pulses (trend $p = 0.18$ and 0.09, respectively). The associations became weaker after multivariate adjustment in all three vegetable groups. There was a weak nonsignificant inverse association between stomach cancer risk and raw vegetables and raw leafy vegetables. The test for trend was not significant either. After multivariate adjustment, these weak associations disappeared completely. For brassicas and prepared leafy vegetables, there was no association with stomach cancer risk in both age- and sex-adjusted and multivariate analysis.

The age- and sex-adjusted rate ratios for total fruit were all lower than one (rate ratios for increasing quintiles were 1.00, 0.92, 0.88, 0.74, and 0.83, respectively), but the trend test was not statistically significant (trend $p = 0.14$). After multivariate adjustment, the rate ratios became closer to unity. The consumption of citrus fruit and of apples and pears was significantly inversely associated with stomach cancer risk in age- and sex-adjusted analyses (trend $p = 0.03$ and 0.05, respectively). However, after multivariate adjustment, these associations were no longer statistically significant. Separate analyses in men only revealed similar findings as compared with the entire group (data not shown).

The rate ratio for both total vegetables and fruit consumption, as continuous variables, for an increment of 25 g/day was 0.98 with a 95 percent confidence interval just including one (table 4). For raw endive and gherkins, a statistically significant negative association and, for spinach, a statistically significant positive association with stomach cancer risk were observed in models with all confounders and excluding or including total vegetables. Rate ratios for other specific vegetables were close to one (e.g., cauliflower, grapefruit), below one (e.g., cabbage, mandarins), or higher than one (e.g., raw carrots, grapes), but the 95 percent confidence intervals never excluded one. When total vegetables or fruit was included in the model, apparent inverse associations disappeared, and rate ratios that were higher than one moved farther away from one.

TABLE 1. Mean daily vegetable and fruit consumption (in grams) in stomach cancer cases and subcohort members by sex, Netherlands Cohort Study, 1986–1992

	Vegetable consumption			
	Men		Women	
	Cases (*n* = 208)	Subcohort (*n* = 1,456)	Cases (*n* = 57)	Subcohort (*n* = 1,497)
Total vegetables	182.0 (80.6)†	187.1 (76.3)	176.2 (79.2)	191.0 (74.5)
Prepared vegetables	148.5 (68.5)	150.8 (63.1)	134.8 (59.1)	149.5 (59.3)
Raw vegetables*	33.5 (25.4)	36.2 (29.0)	41.4 (31.3)	41.5 (29.8)
Brassicas	33.3 (21.9)	32.7 (20.3)	28.4 (20.1)	31.6 (20.0)
Brussels sprouts	8.0 (7.3)	7.7 (6.7)	6.5 (5.9)	7.7 (7.4)
Cauliflower	14.6 (11.4)	14.6 (11.1)	12.8 (10.3)	13.9 (10.5)
Cabbage (white/green)	6.9 (8.3)	7.2 (8.2)	6.2 (7.7)	6.9 (8.0)
Kale	3.7 (3.9)	3.3 (3.4)	2.9 (3.6)	3.2 (3.4)
Pulses*,‡	32.9 (23.3)	34.7 (23.0)	26.4 (18.3)	30.7 (20.7)
String/French beans*	19.9 (17.4)	20.5 (15.3)	15.2 (10.7)	19.5 (14.7)
Broad beans	5.0 (7.1)	4.7 (7.2)	3.6 (6.0)	4.3 (6.6)
Leafy vegetables, prepared	23.4 (17.7)	21.6 (16.0)	19.2 (18.2)	21.3 (14.9)
Spinach	11.0 (10.5)	9.6 (8.9)	8.6 (8.4)	9.4 (8.3)
Endive	12.4 (10.4)	12.0 (10.8)	10.6 (12.9)	11.9 (10.2)
Leafy vegetables, raw	8.4 (7.1)	9.9 (9.2)	9.1 (8.6)	10.1 (8.4)
Endive	1.5 (2.9)	2.4 (4.9)	2.2 (4.2)	2.5 (4.3)
Lettuce	6.9 (6.1)	7.6 (6.7)	6.9 (6.5)	7.6 (6.6)
Other vegetables				
Carrots, prepared	8.4 (7.4)	9.0 (8.9)	7.1 (6.5)	8.9 (8.6)
Carrots, raw*	1.4 (4.6)	2.1 (7.8)	5.1 (13.8)	3.5 (9.4)
Sweet peppers*	2.1 (3.5)	2.5 (4.0)	2.8 (3.8)	3.3 (4.9)
Tomatoes*	19.8 (20.1)	19.5 (20.1)	24.4 (21.1)	23.5 (20.3)
Red beets*	7.3 (7.4)	7.7 (8.7)	7.0 (7.2)	8.1 (7.7)
Sauerkraut	6.2 (6.0)	5.9 (5.5)	4.4 (3.8)	5.7 (4.9)
Mushrooms*	2.8 (3.6)	3.2 (3.9)	3.0 (4.6)	3.7 (4.4)
Gherkins	1.0 (2.1)	1.9 (8.1)	0.8 (2.5)	1.8 (6.6)
Rhubarb	1.9 (5.0)	2.2 (5.7)	2.4 (5.9)	2.4 (5.4)
	Fruit consumption			
	Men		Women	
	Cases (*n* = 219)	Subcohort (*n* = 1,525)	Cases (*n* = 63)	Subcohort (*n* = 1,598)
Total fruit*	144.9 (103.2)	154.9 (111.8)	186.6 (111.0)	196.1 (118.9)
Citrus fruit*	56.0 (63.3)	64.8 (69.8)	90.5 (79.2)	88.2 (73.2)
Oranges*	39.6 (50.8)	40.6 (51.1)	57.1 (58.0)	55.9 (55.8)
Mandarins*	3.5 (5.8)	3.8 (7.2)	4.3 (9.7)	5.5 (8.9)
Grapefruit*	4.4 (15.0)	6.6 (21.7)	14.7 (35.7)	11.4 (26.3)
Processed orange/grapefruit juice*	8.4 (32.1)	13.8 (38.2)	14.3 (29.2)	15.3 (35.4)
Apples, pears*	62.1 (71.7)	67.4 (74.6)	72.9 (69.7)	84.2 (82.0)
Bananas	12.2 (23.7)	12.9 (25.0)	12.7 (23.2)	12.9 (26.8)
Strawberries*	6.5 (7.6)	6.8 (7.8)	7.4 (6.6)	8.1 (8.6)
Grapes*	4.0 (8.5)	3.9 (8.5)	5.0 (7.6)	5.0 (9.7)
Dried fruit*	0.4 (1.3)	0.7 (3.2)	1.2 (2.6)	0.9 (2.8)
Other fruit*	6.7 (25.7)	8.0 (29.0)	10.6 (25.6)	13.5 (36.0)
Other fruit juices*	6.7 (25.6)	7.8 (28.7)	10.3 (25.3)	12.8 (34.2)

* p value (Mann-Whitney U test comparing subcohort means between men and women) < 0.05.
† Numbers in parentheses, standard deviation.
‡ In this group, dried seeds also were included.

There was an increase in the mean consumption of vegetable and fruit consumption combined and of total vegetables in stomach cancer cases diagnosed in the later years of follow-up (table 5). The mean fruit consumption in each of the case groups fluctuated but showed no clear trend. Cases diagnosed in the first year of follow-up and those diagnosed in the first 2 years of follow-up consumed significantly less total vegetables than did cases diagnosed in later years of follow-up ($p < 0.001$).

TABLE 2. Mean intake of total vegetables and fruit (g/day) in the subcohort for several characteristics for men and women together, Netherlands Cohort Study, 1986–1992

Characteristics	Vegetable consumption		Fruit consumption	
	n = 2,953	g/day	n = 3,123	g/day
Age (years)				†
55–59	1,132	187	1,198	149
60–64	1,025	189	1,082	155
65–69	796	185	843	161
Cigarette smoking status		*		***
Never	1,026	210	1,090	132
Exsmoker	1,016	212	1,061	120
Current smoker	911	206	972	94
Educational level‡		*		**
Primary school/lower vocational	1,501	204	1,616	87
Secondary school/medium vocational	1,034	210	1,080	95
University/higher vocational	398	209	406	92
Stomach disorders		**		***
No	2,676	208	2,832	92
Yes	277	196	291	66
Family history of stomach cancer				
No	2,754	207	2,913	92
Yes	199	202	210	97
Fruit consumption		***		
Quintile 1	606	200		
Quintile 2	593	219		
Quintile 3	605	220		
Quintile 4	584	233		
Quintile 5	565	247		
Vegetable consumption				***
Quintile 1			624	50
Quintile 2			629	73
Quintile 3			629	80
Quintile 4			626	90
Quintile 5			615	127

* p value (analysis of variance comparing means adjusted for age and sex) < 0.05; ** p < 0.01; *** p < 0.001.

† p value (analysis of variance comparing means adjusted for sex) < 0.01.

‡ Because of missing values, the numbers do not add up to 2,953 or 3,123.

For vegetable and fruit consumption combined, table 6 shows that, after exclusion of stomach cancer cases diagnosed in the first year of follow-up, the rate ratios for the second to the fifth quintiles were closer to the null value (0.84, 0.79, 0.95, and 0.81, respectively; trend p = 0.51) than were those for the entire group (table 3). If we limited our analyses to the cases diagnosed in the first year of follow-up, a strongly reduced stomach cancer risk with increasing tertile of intake was observed (rate ratio of the highest to lowest tertile = 0.49, 95 percent confidence interval 0.20–1.18, trend p = 0.06). This inverse association could be attributed exclusively to the lower vegetable consumption of the first year cases; that is, the rate ratios and 95 percent confidence intervals for increasing tertiles of total vegetable consumption were 1.00, 0.17 (0.06–0.50), and 0.18 (0.06–0.54), trend p = 0.0001, while these were 1.00, 0.84 (0.34–1.90), and 1.01 (0.42–2.41), trend p = 0.96, for total fruit consumption. When cases diagnosed in the first or second year of follow-up were combined (n = 70 cases), similar associations were found (data not shown). For subjects without stomach disorders, rate ratios were almost all similar to those found in the entire group. In contrast, for subjects with stomach disorders, a reduced stomach cancer risk with increasing tertile of intake was

TABLE 3. Rate ratios (RRs) and 95% confidence intervals (CIs) of stomach cancer according to intake of vegetables and fruit (categorical analyses), Netherlands Cohort Study, 1986–1992

	Median intake (g/day)	No. of cases of stomach cancer	No. of person-years	RR, age and sex adjusted	Multivariate RR
Total vegetables and fruit combined					
Quintile					
1 (low)*	190.0	75	3,503	1.0	1.0†
2	276.0	51	3,567	0.70 (0.48–1.02)‡	0.74 (0.50–1.09)
3	345.0	47	3,577	0.65 (0.45–0.96)	0.69 (0.47–1.03)
4	418.0	51	3,599	0.76 (0.52–1.11)	0.81 (0.55–1.20)
5 (high)	544.0	40	3,620	0.64 (0.43–0.97)	0.72 (0.48–1.10)
Test for trend *p* value				0.04	0.14
Total vegetables					
Quintile					
1 (low)	103.0	72	3,511	1.00	1.00§
2	145.0	57	3,593	0.76 (0.52–1.09)	0.81 (0.55–1.18)
3	178.0	33	3,573	0.47 (0.31–0.72)	0.51 (0.33–0.80)
4	217.0	44	3,546	0.64 (0.43–0.95)	0.71 (0.47–1.07)
5 (high)	286.0	58	3,643	0.79 (0.55–1.14)	0.86 (0.58–1.26)
Test for trend *p* value				0.10	0.25
Prepared vegetables					
Quintile					
1 (low)	79.0	70	3,490	1.00	1.00§
2	114.0	51	3,568	0.70 (0.48–1.03)	0.73 (0.49–1.08)
3	142.0	36	3,577	0.49 (0.32–0.75)	0.52 (0.34–0.81)
4	174.0	47	3,573	0.68 (0.46–1.00)	0.72 (0.48–1.08)
5 (high)	231.0	60	3,657	0.79 (0.55–1.14)	0.81 (0.56–1.19)
Test for trend *p* value				0.18	0.26
Raw vegetables					
Quintile					
1 (low)	8.0	68	3,547	1.00	1.00§
2	22.0	49	3,567	0.69 (0.47–1.02)	0.78 (0.52–1.16)
3	33.0	54	3,520	0.89 (0.61–1.30)	1.02 (0.69–1.51)
4	47.0	45	3,602	0.73 (0.49–1.09)	0.84 (0.56–1.27)
5 (high)	74.0	48	3,630	0.81 (0.55–1.19)	0.97 (0.64–1.46)
Test for trend *p* value				0.33	0.96
Pulses					
Quintile					
1 (low)	10.0	59	3,254	1.00	1.00§
2	19.0	54	3,645	0.82 (0.56–1.21)	0.82 (0.55–1.22)
3	28.0	39	3,620	0.52 (0.34–0.80)	0.54 (0.35–0.84)
4	39.0	59	3,771	0.78 (0.53–1.14)	0.81 (0.54–1.20)
5 (high)	60.0	53	3,575	0.71 (0.48–1.05)	0.70 (0.47–1.06)
Test for trend *p* value				0.09	0.10

Table continues

TABLE 3. Continued

	Median intake (g/day)	No. of cases of stomach cancer	No. of person-years	RR, age and sex adjusted	Multivariate RR
			Brassicas		
Quintile					
1 (low)	10.0	48	3,342	1.00	1.00§
2	20.0	62	3,447	1.28 (0.86–1.90)	1.32 (0.88–1.99)
3	27.0	51	3,633	0.92 (0.61–1.39)	0.95 (0.62–1.45)
4	38.0	53	3,808	0.94 (0.63–1.42)	0.98 (0.64–1.49)
5 (high)	58.0	50	3,636	0.91 (0.60–1.37)	0.93 (0.61–1.43)
Test for trend *p* value				0.24	0.29
			Leafy vegetables, prepared		
Quintile					
1 (low)	4.0	53	3,592	1.00	1.00§
2	12.0	52	3,512	0.91 (0.61–1.36)	0.94 (0.63–1.43)
3	19.0	50	3,229	1.00 (0.67–1.51)	1.05 (0.69–1.59)
4	26.0	57	3,918	1.01 (0.68–1.49)	1.02 (0.68–1.53)
5 (high)	41.0	52	3,615	0.93 (0.62–1.39)	0.96 (0.63–1.44)
Test for trend *p* value				0.94	0.98
			Leafy vegetables, raw		
Tertile					
1 (low)	3.0	106	6,399	1.00	1.00§
2	8.0	90	5,926	0.98 (0.73–1.32)	1.08 (0.79–1.47)
3 (high)	18.0	86	5,539	0.78 (0.57–1.07)	0.90 (0.64–1.25)
Test for trend *p* value				0.12	0.76
			Total fruit		
Quintile					
1 (low)	46.0	74	3,803	1.00	1.00¶
2	109.0	59	3,707	0.92 (0.64–1.32)	0.98 (0.68–1.43)
3	157.0	57	3,837	0.88 (0.61–1.27)	0.94 (0.65–1.38)
4	216.0	46	3,743	0.74 (0.50–1.09)	0.80 (0.54–1.20)
5 (high)	325.0	45	3,797	0.83 (0.56–1.23)	0.97 (0.64–1.48)
Test for trend *p* value				0.14	0.51
			Citrus fruit		
Quintile					
1 (low)	3.0	78	3,800	1.00	1.00¶
2	28.0	63	3,809	0.87 (0.61–1.23)	0.95 (0.66–1.36)
3	64.0	64	4,255	0.84 (0.59–1.19)	0.92 (0.64–1.33)
4	100.0	31	3,235	0.60 (0.39–0.93)	0.70 (0.44–1.10)
5 (high)	175.0	45	3,738	0.75 (0.51–1.11)	0.86 (0.57–1.29)
Test for trend *p* value				0.03	0.20

Table continues

observed (rate ratio of the highest to lowest tertile = 0.48, 95 percent confidence interval 0.19–1.19, trend $p = 0.09$).

DISCUSSION

We found evidence for an inverse association between stomach cancer risk and the consumption of vegetables and fruit combined, total vegetables, pulses, raw leafy vegetables, total fruit, citrus fruit, and apples and pears in age- and sex-adjusted analyses, which became weaker and nonsignificant in multivariate analyses. In 30 analyses of specific vegetables and fruit, we found statistically significant inverse associations for raw endive and gherkins and a statis-

TABLE 3. Continued

	Median intake (g/day)	No. of cases of stomach cancer	No. of person-years	RR, age and sex adjusted	Multivariate RR
			Apples and pears		
Quintile					
1 (low)	0.0	87	4,363	1.00	1.00¶
2	45.0	74	5,133	0.75 (0.54–1.05)	0.79 (0.57–1.11)
3	80.0	40	2,890	0.79 (0.53–1.17)	0.85 (0.57–1.28)
4	116.0	54	4,222	0.71 (0.49–1.01)	0.79 (0.54–1.14)
5 (high)	232.0	26	2,279	0.70 (0.44–1.11)	0.76 (0.47–1.23)
Test for trend *p* value				0.05	0.18

* Reference category.
† *The model included age, sex, smoking, education, stomach disorders, and family history of stomach cancer.*
‡ Numbers in parentheses, 95% CI.
§ The model included age, sex, smoking, education, stomach disorders, family history of stomach cancer, and total fruit consumption (g/day).
¶ The model included age, sex, smoking, education, stomach disorders, family history of stomach cancer, and total vegetable consumption (g/day).

tically significant positive association for spinach, which all must be regarded cautiously because of multiple testing. Analyses limited to cases occurring in the first year of follow-up revealed a strong reduced stomach cancer risk with increasing vegetable and fruit consumption combined. For subjects with stomach disorders, a reduced risk with increasing vegetable and fruit consumption combined was also found.

This cohort study was conducted in a large sample of men and women from the general Dutch population. After 6.3 years of follow-up, the number of stomach cancer cases identified ($n = 282$) should be sufficient to detect a large effect if present. One of the strengths of our study is the high degree of completeness of follow-up of both person-years and cancer cases, indicating that selection bias due to loss to follow-up is unlikely. Another strength with the prospective design is that the diet is measured before the disease is diagnosed, thus avoiding the problem of biased recall of dietary habits. A fact that could have influenced the results is that people with preclinical symptoms of stomach carcinoma or stomach disorders might have changed their dietary habits months or years before the baseline measurement. Therefore, we compared results of analyses in which we excluded cases diagnosed during the first year of follow-up or subjects with stomach disorders with analyses of the total group. In multivariate analyses, adjustment was made for all measured variables that were associated with stomach cancer risk. However, it is possible that unmeasured or unidentified risk factors may have affected the study results. We could not adjust for *Helicobacter pylori* infection because this was not measured in 1986. The prevalence of antibodies to *H. pylori* is about 50 percent in healthy Dutch people aged 50–70 years (22). We can only speculate that a certain proportion of our study subjects with stomach disorders (e.g., peptic ulcer, gastritis) may be infected with *H. pylori* and as a consequence have lowered their vegetable and fruit consumption. However, subjects without severe stomach disorders may also be infected but did not change their dietary habits. Stratified analyses (on stomach cancer and vegetable and fruit consumption combined) by subjects with and without stomach disorders revealed a stronger association in subjects with stomach disorders. Thus, subjects with and without stomach disorders should be regarded as separate groups in analyses.

A potential limitation of our study is the possibility of misclassification of exposure. Particularly, the estimation of the frequency of consumption of a wide range of vegetables in both summer and winter as well as the estimation of the portion size is rather difficult. It is therefore possible that participants to some degree have under- or overestimated their actual intake. This possible nondifferential misclassification would have resulted in bias toward the null value, and consequently the actual risk estimates may have been stronger than those we have observed. We have, however, intended to minimize the amount of uninformative data. Subjects with incomplete or inconsistent dietary data and, specifically, those subjects who appeared not to have understood how to answer the questions on vegetable consumption were excluded. The correlation coefficient for total vegetable consumption is rather low but comparable to the figures reported for other prospective studies (23–25). A reason for the low correlation may be the relative lack of contrast in the

TABLE 4. Rate ratios (RRs) and 95% confidence intervals (CIs) for continuous estimates of vegetable and fruit intake (total and specific types), Netherlands Cohort Study, 1986–1992

Vegetables or fruit variables	RR/25 g*	95% CI	RR/25 g†	95% CI
Total vegetables‡	0.98	0.94–1.02		
Brussels sprouts	1.03	0.65–1.65	1.18	0.70–1.98
Cauliflower	0.97	0.72–1.31	1.05	0.75–1.47
Cabbage (white/green)	0.87	0.57–1.31	0.93	0.59–1.48
Kale	1.70	0.70–4.14	2.13	0.83–5.47
String/French beans	0.85	0.67–1.07	0.86	0.66–1.12
Broad beans	1.00	0.63–1.58	1.07	0.67–1.73
Spinach	1.40	0.99–1.97	1.66	1.12–2.45
Endive, prepared	1.03	0.76–1.39	1.05	0.75–1.47
Endive, raw	0.33	0.12–0.89	0.34	0.12–0.94
Lettuce	0.88	0.52–1.48	0.94	0.55–1.62
Carrots, prepared	0.79	0.52–1.21	0.83	0.52–1.32
Carrots, raw	1.12	0.75–1.67	1.18	0.78–1.78
Sweet peppers	0.82	0.34–1.95	0.94	0.37–2.37
Tomatoes	1.07	0.91–1.26	1.16	0.96–1.40
Red beets	0.76	0.50–1.16	0.79	0.50–1.25
Sauerkraut	0.92	0.51–1.67	1.04	0.54–2.00
Mushrooms	0.80	0.33–1.97	0.89	0.35–2.25
Gherkins	0.29	0.09–0.91	0.30	0.09–0.95
Rhubarb	0.82	0.43–1.57	0.84	0.44–1.61
Total fruit§	0.98	0.96–1.01		
Oranges	1.00	0.94–1.06	1.02	0.95–1.10
Mandarins	0.83	0.53–1.32	0.87	0.55–1.39
Grapefruit	0.98	0.85–1.13	1.00	0.86–1.17
Apples, pears	0.97	0.93–1.02	0.98	0.92–1.05
Bananas	0.97	0.85–1.10	0.98	0.86–1.12
Strawberries	0.87	0.58–1.32	0.91	0.60–1.39
Grapes	1.06	0.75–1.48	1.12	0.79–1.59
Orange/grapefruit juice	0.92	0.82–1.03	0.92	0.82–1.03
Other fruit juice	0.95	0.84–1.07	0.95	0.84–1.08
Dried fruit	0.54	0.13–2.23	0.57	0.14–2.37
Other fruit	0.95	0.84–1.07	0.95	0.84–1.07

* Adjusted for age, sex, smoking, education, stomach disorders, family history of stomach cancer, and total fruit consumption (for vegetables' variables) or total vegetable consumption (for fruit variables).

† Adjusted for age, sex, smoking, education, stomach disorders, family history of stomach cancer, total fruit consumption (g/day), and total vegetable consumption (g/day).

‡ Adjusted for age, sex, smoking, education, stomach disorders, family history of stomach cancer, and total fruit consumption (g/day).

§ Adjusted for age, sex, smoking, education, stomach disorders, family history of stomach cancer, and total vegetable consumption (g/day).

frequency of total vegetable consumption (as indicated by a coeffient of variation of approximately 40 percent). In the Dutch population, people are accustomed to a diet including one hot meal per day, which almost always includes vegetables. However, because of personal preferences, the contrast is much higher for specific vegetables (the coefficient of variation is approximately 100 percent) and, therefore, a smaller measurement error is to be expected. Fruit consumption is easier to estimate, and the contrast in the fruit consumption was high (about a sixfold difference between the highest and lowest quintiles) (coefficient of variation is approximately 70 percent) and large enough to detect an effect. Moreover, in this study population, an inverse association between vegetables and fruit and lung cancer risk has been found, which shows that it is possible to detect associations using our semiquantitative food questionnaire (26).

Our findings are quite comparable to findings of other prospective studies, but they do not support findings of case-control studies, which showed a more consistent and a strong protective effect of vegetable and fruit consumption. The six prospective studies that have investigated the effect of vegetable and fruit consumption on stomach cancer did not yield consistent results. A large Japanese study (5,247 stomach cancer cases) reported a significant negative association for green-yellow vegetables and stomach cancer

TABLE 5. Mean daily consumption of total vegetables and fruit combined (V&F), total vegetables, and total fruit in stomach cancer cases according to year of follow-up, Netherlands Cohort Study, 1986–1992

Group*	V&F		Total vegetables		Total fruit	
	No. of cases	Mean g/day	No. of cases	Mean g/day	No. of cases	Mean g/day
All cases	265	335.7 (146.7)†	265	180.8 (80.2)	282	154.2 (106.2)
Year of follow-up‡						
1	31	293.6 (142.5)	31	138.6 (75.0)	34	155.0 (103.7)
2	39	307.8 (138.3)	39	166.5 (78.9)	40	143.1 (90.3)
3	36	348.6 (139.8)	36	176.6 (63.0)	41	162.6 (125.8)
4	47	340.6 (132.4)	47	182.8 (8.0)	48	156.1 (97.2)
5	50	379.5 (163.7)	50	208.8 (90.6)	51	170.0 (109.1)
6 + 7	62	327.7 (148.9)	62	189.1 (77.3)	68	142.1 (108.9)

* Mean of consumption in the subcohort was 362.3 (standard deviation (SD), 148.5) g/day (n = 2,953), 189.1 (SD, 75.4) g/day (n = 2,953), and 175.7 (SD, 117.3) g/day (n = 3,123) for V&F, total vegetables, and total fruit, respectively.

† Numbers in parentheses, SD.

‡ p value of Mann-Whitney U test, between the mean intake of the first and following years of follow-up, was 0.06, 0.0005, and 0.89 for V&F, total vegetables, and total fruit, respectively.

TABLE 6. Multivariate rate ratios (RRs) and 95% confidence intervals (CIs) of stomach cancer according to quintiles or tertiles of combined vegetable and fruit intake (V&F, g/day), Netherlands Cohort Study, 1986–1992

V&F	Median intake (g/day)	No. of cases	Person-years	RR	95% CI	Test for trend p value
			*Exclusion of cases diagnosed in first year of follow-up**			
Quintile 1†	190.0	60	2,916	1.00		
Quintile 2	276.0	46	2,979	0.84	0.55–1.26	
Quintile 3	345.0	43	2,985	0.79	0.52–1.19	
Quintile 4	418.0	48	3,009	0.95	0.63–1.43	
Quintile 5	554.0	36	3,018	0.81	0.52–1.26	0.51
			*Analysis restricted to cases detected in the first year of follow-up**			
Tertile 1†	226.0	18	962	1.00		
Tertile 2	345.0	6	995	0.37	0.15–0.94	
Tertile 3	493.0	7	967	0.49	0.20–1.18	0.06
			Subjects without stomach disorders‡			
Quintile 1†	192.0	57	3,035	1.00		
Quintile 2	275.0	40	3,181	0.75	0.49–1.15	
Quintile 3	346.0	38	3,291	0.67	0.44–1.04	
Quintile 4	418.0	44	3,323	0.88	0.58–1.35	
Quintile 5	555.0	36	3,387	0.76	0.48–1.18	0.35
			Subjects with stomach disorders‡			
Tertile 1†	213.0	26	703	1.0		
Tertile 2	328.0	16	524	0.87	0.43–1.73	
Tertile 3	487.0	7	421	0.48	0.19–1.19	0.09

* Adjusted for age, sex, family history of stomach cancer, stomach disorders, education, and smoking status.

† Reference category.

‡ Adjusted for age, sex, family history of stomach cancer, education, and smoking status.

(rate ratio of daily consumption vs. never = 0.67) (trend p = 0.0008) (5), whereas a smaller Japanese study (57 cases) reported nonsignificant positive associations for both green-yellow vegetables and other vegetables (rate ratios of daily vs. 1–2 times/week were 1.54 and 1.15, respectively) (9). In the Iowa Women's Health Study (26 cases), a nonsignificant inverse association was found for nearly all vegetables and fruit groups (11). In the groups with the highest intake, an approximate halving of the risk was observed. A study among Hawaiians of Japanese descent (150 cases) found a nonsignificant reduction in risk for total vegetables, green vegetables, and cruciferous vegetables (6, 7). The rate ratios (high consumption vs. never) were 0.7 for all three vegetable groups. Two other studies conducted in the United States (75 cases) and China (539 cases) reported no association for total vegetables (8, 10). For fruit consumption, positive as well as inverse and no associations with stomach cancer risk have been reported in prospective studies (6–11). The relative risks reported for subjects with the highest versus lowest consumption varied from 0.6 (6) to 1.9 (9), while the contrast in fruit consumption varied from large (>301 g/day vs. 0) (6) to small (daily vs. 1–2 times/week) (9). In these studies, adjustment was made for age and sex (5–7, 9), age and smoking (8), or age, education, and smoking (11). None of these studies assessed the independent effect of specific vegetable or fruit groups by adjusting for total vegetables or fruit. When in the Netherlands Cohort Study both dietary and nondietary potential confounders were added in the multivariate model, some of the weak nonsignificant inverse associations (e.g., raw vegetables) disappeared completely. Thus, insufficient adjustment for potential confounders could have led to a seemingly stronger protective effect in some other studies. In the Netherlands Cohort Study, quite detailed information was gathered on vegetable and fruit consumption. In some of the other prospective studies, rather short questionnaires with few items on vegetables and fruit consumption were used (5, 9).

Specific methodological shortcomings of case-control studies may explain the discrepancies between results of prospective studies and case-control studies. One of the major problems of case-control studies is the possibility of recall bias due to knowledge of the disease status. It has been shown that recall of past dietary intake can be influenced by current dietary habits (27–29). Furthermore, cases might have changed their dietary habits as a consequence of their disease or its precursors (e.g., gastritis). Many case-control studies obtained information about the food habits of cases (less than) 1 year before the time of diagnosis of cancer or the onset of symptoms. In our study, we showed that, in the last year or 2 years before the diagnosis of stomach cancer, subjects consumed less vegetables than did those who were diagnosed in later years. When we included only these cases in analyses, as is done in case-control studies, we found a strong inverse association between vegetable consumption and stomach cancer risk similar to the findings in many case-control studies.

A reason for a reduced consumption of vegetables, but not fruit consumption, may be that people with preclinical symptoms of stomach cancer have an aversion to hot meals in which vegetables are usually eaten. We could confirm this because these cases also had a reduced intake of meat, fish, and potatoes mostly eaten with vegetables in a hot meal (data not shown).

The finding of only a weak effect of vegetable and fruit consumption on stomach cancer risk could also be explained by a relatively high intake of vegetables and fruit in the Dutch population. In the Dutch National Food Consumption Survey of 1987–1988, the mean daily vegetable consumption in men and women aged 50–64 years was 165.8 and 163.5 g and, for fruit, 129.4 and 162.3 g, respectively (30). In a recently published cohort study in Wales, the mean daily intake of vegetables and fruit was 40–50 percent lower (118 and 83 g, respectively) than in our study (31). In this study, a significant protective effect against digestive tract cancer (of which 30 percent were stomach cancer cases) for fruit was found (rate ratio of the highest to lowest category of intake = 0.4, 95 percent confidence interval 0.1–0.8) but not for vegetables (rate ratio of the highest to lowest category of intake = 0.7, 95 percent confidence interval 0.3–1.5). In another study, total vegetable intake was significantly inversely associated (mean vegetable intake was 76.8 g/day), and fruit intake was nonsignificantly associated with stomach cancer risk (mean fruit intake was 218.4 g/day) (6). This may imply that, when the intake is lower than a certain threshold level, a risk-reducing effect may be expected.

In conclusion, a clear protective effect of vegetable consumption against stomach cancer was not found in the Dutch population. The Netherlands Cohort Study was more in line with the findings of other prospective studies than with those of case-control studies. Methodological limitations of case-control studies, particularly information bias, may have resulted in an observed strong protective effect of vegetable and fruit consumption against stomach cancer in these studies. Using the present data, we were not able to study sex differences in the associations, but it may be worthwhile to repeat the analyses after more years of follow-up because of differences in the amount and types of vegetables and fruit consumed between men and women.

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