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Plant sterol intakes and colorectal cancer risk in the Netherlands Cohort Study on Diet and Cancer[1–3]

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ABSTRACT

Background: Plant sterols in vegetable foods might prevent colorectal cancer.

Objective: The objective was to study plant sterol intakes in relation to colorectal cancer risk in an epidemiologic study.

Design: The study was performed within the framework of the Netherlands Cohort Study on Diet and Cancer in 120 852 subjects who completed a baseline questionnaire in 1986. After 6.3 y of follow-up, 620 colon and 344 rectal cancer cases were detected. A case-cohort approach was used to calculate confounder-adjusted rate ratios (RRs) and their 95% CIs for quintiles of plant sterol intake.

Results: The total mean (±SD) intake of campesterol, stigmasterol, β-sitosterol, campestanol, and β-sitostanol was 285 ± 97 mg/d. Major contributors to plant sterol intake were bread (38%), vegetable fats (26%), and fruit and vegetables (21%). For men, there was no clear association between intake of any of the plant sterols and colon cancer risk when age, smoking, alcohol use, family history of colorectal cancer, education level, and cholecystectomy were controlled for. Adjustment for energy did not alter the result. For rectal cancer, adjustment for energy resulted in positive associations between risk and campesterol and stigmasterol intakes. For women, there was no clear association between intake of any of the plant sterols and colorectal cancer risk.

Conclusion: A high dietary intake of plant sterols was not associated with a lower risk of colon and rectal cancers in the Netherlands Cohort Study on Diet and Cancer. *Am J Clin Nutr* 2001;74:141–8.

KEY WORDS Plant sterols, phytosterols, colon cancer, rectal cancer, bread, vegetable fat, prospective study, Netherlands Cohort Study on Diet and Cancer

See corresponding editorial on page 4.

INTRODUCTION

Plant sterols are bioactive components of all foods of vegetable origin (1). They are 28- or 29-carbon alcohols that are structurally similar to the 27-carbon alcohol cholesterol (2). The dominant dietary plant sterols β-sitosterol, campesterol, and stigmasterol are classified as 4-desmethylsterols of the cholestane series, all of which have double bonds at the C-5 position of the ring (3). In certain structures this double bond is saturated and these compounds are referred to as plant stanols. Examples of stanols are β-sitostanol and campestanol, which exist in quantifiable amounts in cereals and fruit and vegetables, but generally in lower concentrations than the unsaturated plant sterols (4).

Compared with the general population, Seventh-day Adventists have lower rates of cancer at many sites (including colorectal cancer), higher dietary intakes of plant sterols, and a lower bile acid excretion (5). Because bile acids were reported to be tumor promotors in colon cancer (6), it was hypothesized that decreased bile acid excretion is a physiologic response to high intakes of plant sterols (7). Supplementation with plant sterols in sterol balance studies, however, gave conflicting results (8–13). Thus, strong support for decreased bile acid excretion induced by a higher intake of plant sterols was not shown, even though the small sample size and the lack of controlled dietary intervention studies made it difficult to rule out the possibility. Studies in rats showed evidence of an alternative explanation to a preventive effect of plant sterols. Rats that consumed an experimental diet mixed with β-sitosterol and the chemical carcinogen methylnitrosurea had a significantly lower incidence of tumors than did controls who consumed the carcinogen only (14). This was found despite no differences in bile acid excretion between the 2 groups. Because it is not clear whether β-sitosterol exerted its effect without the carcinogen, Janezic and Rao (15) studied the effect of a diet enriched with sitosterol on colonic mucosal cell proliferation in mice. There was a dose-dependent decrease in cell proliferation during controlled cholic acid supplementation after increasing doses of β-sitosterol. This finding was confirmed by Awad et al (16), who found significantly lower cell proliferation in rats fed a mixture of cholic acid and plant sterols than in control rats fed cholic acid only. Moreover, the growth

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of human cancer cells in culture (17) and when xenografted in mice (18) was inhibited by plant sterols.

No prospective epidemiologic studies of plant sterol intake in relation to colorectal cancer have been conducted. It is hypothesized that humans with a high intake of dietary plant sterols, especially β-sitosterol, have a decreased risk of colon and rectal cancers. Therefore, the aim of this study was to investigate the association between different plant sterol intakes and risk of colorectal cancer in a prospective cohort study.

SUBJECTS AND METHODS

Study population and follow-up of cancer

The investigation was performed within the framework of the Netherlands Cohort Study on Diet and Cancer (19), the original aim of which was to study the association between dietary factors and the development of cancer. The cohort consisted of 120 852 subjects (48% men and 52% women) aged 55–69 y who completed a baseline questionnaire in 1986. A case-cohort approach was used for data processing and analysis. Case subjects were thereby enumerated from the entire cohort, whereas the person-years at risk were estimated from a random sample of 3500 subjects (1688 men and 1812 women). This subcohort was chosen immediately after the baseline exposure measurements were made and no subcohort member was lost to follow-up. The study design was described in detail elsewhere (19). The design used is effective for reducing costs in large cohort studies because exposure information collected for the entire cohort is processed for the cases and the subcohort only.

Follow-up of colon and rectal cancers was established by using a combination of a computerized linkage system to all 9 cancer registries in the Netherlands and a nationwide pathology database (20). The follow-up was restricted to the period from baseline to December 1992, a total of 6.3 y. Completeness of the follow-up was estimated to be >96% (21). After exclusion of all prevalent cancer cases other than nonmelanoma skin cancer, a total of 620 colon (332 men and 288 women) and 344 rectal (217 men and 127 women) cancer cases was detected in the entire cohort of 3346 remaining subcohort subjects. Furthermore, subjects with incomplete and inconsistent dietary data were not included in the analysis, resulting in a final subcohort of 3123 subjects (1525 men and 1598 women), 574 colon cancer cases (303 men and 271 women), and 317 rectal cancer cases (201 men and 116 women).

Semiquantitative food-frequency questionnaire

The subjects completed a semiquantitative food-frequency questionnaire that included 150 food items and covered subjects' food habits during the year before the start of the study. The principal nutrients of interest were energy, protein, fat, cholesterol, carbohydrates, dietary fiber, alcohol, vitamin A, β-carotene, and vitamin C. Intake of dietary plant sterols was covered by questions on fruit, vegetables, potatoes, bread, grains, grain products, cakes, cookies, chocolate, nuts, seeds, peanut butter, and vegetable fats. Moreover, details of types and brands of vegetable fats and oils used in cooking as spreads and as salad dressings proved useful for estimating plant sterol intakes. Daily mean nutrient intakes were calculated by using the computerized Dutch food-composition table of 1986 (22).

The questionnaire was validated and tested for reproducibility (23, 24). The results indicated that the questionnaire adequately covered food groups such as bread and added fats. The questionnaire was especially reliable for indicating the type of fat intake because detailed brand information was included. The validation study of the questionnaire showed high correlation coefficients for polyunsaturated fat ($r = 0.75$), dietary fiber ($r = 0.74$), and bread ($r = 0.80$) intakes (23). Misclassification of plant sterol intakes could not be ruled out. However, because plant sterols share their food sources with those of the other food components mentioned, the questionnaire likely adequately ranked subjects according to plant sterol intake.

Preparation of the plant sterol database

Plant sterols in food were analyzed at the Department of Clinical Nutrition, Göteborg, Sweden. The analytic method used was a modification of the procedure used by Jonker et al (25), which involved acid hydrolysis, alkaline saponification, lipid extraction, silylation, detection, and quantification with gas-liquid chromatography. Five frequently occurring plant sterols were measured: the unsaturated plant sterols campesterol, stigmasterol, and β-sitosterol and the saturated plant stanols campestanol and β-sitostanol. The sterol content of 229 Swedish food items (78 vegetables, 41 fruit, 60 cereal products, 40 vegetable oils and margarines, and 10 types of cookies and cakes) corresponding to foods in the Swedish food-composition table was measured. To restrict the cost and duration of the study, the Swedish values for fruit and vegetables, cereal products, nuts, and some oils that were similar to Dutch food products were transferred to the Netherlands Cohort Study on Diet and Cancer database. In addition, Dutch food items with a high consumption or with an assumed high concentration of plant sterols (ie, food products with a high vegetable fat content) were analyzed. In total, 63 food items of Dutch origin were analyzed: 28 cooking fats and spreads, 4 vegetables, 12 bread and cake products, 4 mayonnaise products, and 15 other products. All fat samples, except 2 types of oils, were purchased in 1995, before the processing techniques for margarine were changed in Europe to minimize *trans* fatty acid concentrations.

The plant sterol content of all products of pure animal origin was set at zero, as was that of the following products: fruit and vegetable juices, alcoholic drinks, tea, coffee, cocoa drinks, sugar, honey, syrup, molasses, soy sauce, and licorice. The sterol content of food products not analyzed but likely to contain plant sterols was estimated in several ways. For vegetables, we used the cooked value if the raw value was missing and vice versa, without any corrections, because differences in concentrations between raw and boiled vegetables and fruit are small and not consistent (26). For fresh and dried fruit and raw and cooked cereals, the differences in water content were corrected for. The plant sterol content of certain bread products, cookies, pastries, mixed dishes, sweets, and other miscellaneous items was calculated from their ingredients according to common Dutch recipes. The database of plant sterol concentrations was linked to the questionnaire data in the same way as was the data from the Dutch food-composition table.

Statistical analysis

Pearson's correlation coefficients between plant sterol concentrations and certain nutrient intakes were calculated with and without adjustment for energy. Data were analyzed with a case-cohort approach (27); exponentially distributed survival

TABLE 1
Contribution of food groups to the intake of 5 different plant sterols by 3123 men and women of the subcohort[1]

		Unsaturated			Saturated		
	Consumption	Campesterol	β-Sitosterol	Stigmasterol	Campestanol	β-Sitostanol	Total
	g/d	*mg/d*	*mg/d*	*mg/d*	*mg/d*	*mg/d*	*mg/d*
Fruit							
Total	176 ± 117	2.5 ± 2.1	25.3 ± 17.5	1.0 ± 0.8	0	0 ± 0.1	2.8 ± 20.0 [10]
Citrus	62 ± 64	1.9 ± 1.9	11.7 ± 12.3	0.6 ± 0.6	0	0	14.2 ± 14.9 [5]
Apples, pears	87 ± 82	0.3 ± 0.3	9.5 ± 9.9	0.1 ± 0.1	0	0	9.9 ± 10.3 [3]
Other	27 ± 32	0.3 ± 0.4	4.1 ± 4.2	0.3 ± 0.5	0	0 ± 0.1	4.7 ± 5.0 [2]
Vegetables							
Total	194 ± 83	4.8 ± 2.2	20.1 ± 9.0	5.4 ± 2.6	0.1 ± 0.1	0.5 ± 0.2	30.9 ± 13.5 [11]
Cabbage	7 ± 9	2.0 ± 1.3	6.9 ± 4.7	0.5 ± 0.3	0	0	9.4 ± 6.3 [3]
Legumes	25 ± 19	0.5 ± 0.4	2.9 ± 2.3	2.0 ± 1.4	0	0.1 ± 0.1	5.5 ± 3.9 [2]
Leafy	33 ± 20	0.4 ± 0.3	3.6 ± 2.7	1.7 ± 1.3	0	0.1 ± 0	5.8 ± 4.4 [2]
Other	129 ± 59	1.9 ± 1.1	6.7 ± 3.7	1.2 ± 1.1	0.1 ± 0.1	0.3 ± 0.2	10.2 ± 5.6 [4]
Potatoes	125 ± 77	0.3 ± 0.2	3.5 ± 2.3	0.5 ± 0.4	0	0.7 ± 0.5	5.0 ± 3.3 [2]
Bread							
Total	160 ± 67	20.5 ± 9.7	57.1 ± 27.0	3.3 ± 1.7	9.2 ± 5.2	11.3 ± 6.0	101.4 ± 49.3 [36]
Whole-wheat bread	58 ± 73	9.8 ± 12.4	27.3 ± 34.4	1.7 ± 2.1	5.1 ± 6.4	6.0 ± 7.5	49.9 ± 62.8 [18]
Brown bread	65 ± 73	6.9 ± 7.8	19.6 ± 22.2	1.1 ± 1.3	3.2 ± 3.5	4.0 ± 4.6	34.8 ± 39.3 [12]
White bread	20 ± 46	2.0 ± 4.6	5.5 ± 12.3	0.2 ± 0.4	0.5 ± 1.1	0.6 ± 1.4	8.8 ± 19.8 [3]
Rye bread	8 ± 20	0.9 ± 2.3	2.2 ± 5.7	0.2 ± 0.4	0.2 ± 0.7	0.4 ± 1.0	3.9 ± 10.1 [1]
Currant bread	5 ± 9	0.3 ± 0.5	1.0 ± 2.0	0 ± 0.1	0.1 ± 0.1	0.1 ± 0.2	1.5 ± 2.9 [1]
Other	4 ± 7	0.6 ± 1.1	1.5 ± 2.6	0.1 ± 0.2	0.1 ± 0.2	0.2 ± 0.4	2.5 ± 4.5 [1]
Other grain products	2 ± 7	0.7 ± 1.8	2.5 ± 5.9	0.2 ± 0.7	0.2 ± 0.5	0.2 ± 0.6	3.8 ± 9.1 [1]
Cakes, cookies, and chocolate	30 ± 21	3.1 ± 2.1	9.3 ± 6.7	1.8 ± 1.7	0.4 ± 0.4	0.7 ± 0.6	15.3 ± 10.9 [5]
Nuts, seeds, and peanut butter	6 ± 13	1.5 ± 2.6	6.9 ± 12.2	1.1 ± 1.9	0	0.1 ± 0.2	9.6 ± 16.8 [3]
Fat							
Total	46 ± 22	16.2 ± 11.2	48.2 ± 36.5	9.1 ± 6.3	0.5 ± 0.7	0.6 ± 0.5	74.6 ± 52.5 [26]
Margarine, 80% fat	21 ± 21	8.2 ± 8.4	29.7 ± 34.7	5.3 ± 5.9	0.4 ± 0.7	0.4 ± 0.4	44.0 ± 48.6 [15]
Mayonnaise, dressings	4 ± 5	3.9 ± 6.5	6.0 ± 9.2	0.7 ± 0.9	0.1 ± 0.1	0 ± 0.1	10.7 ± 16.6 [4]
Margarine, 40% fat	7 ± 14	1.7 ± 3.4	4.3 ± 8.4	1.4 ± 2.7	0	0.1 ± 0.1	7.5 ± 14.7 [3]
Frying fat	4 ± 8	1.5 ± 3.3	4.1 ± 10.0	0.9 ± 2.3	0 ± 0.1	0.1 ± 0.1	6.6 ± 15.7 [2]
Sunflower oil	1 ± 2	0.4 ± 1.0	2.6 ± 5.8	0.4 ± 0.9	0	0 ± 0.1	3.4 ± 5.2 [1]
Soy oil	1 ± 2	0.3 ± 1.1	0.8 ± 2.9	0.3 ± 1.0	0	0 ± 0.1	1.4 ± 7.8 [1]
Other vegetable oils	0 ± 2	0.2 ± 1.2	0.7 ± 4.0	0.1 ± 0.5	0 ± 0.1	0 ± 0.2	1.0 ± 5.8 [0]
Other	8 ± 14	0	0	0	0	0	0
Other food items	—	2.4 ± 2.0	9.8 ± 7.1	2.5 ± 1.9	0.3 ± 0.3	0.6 ± 0.5	15.6 ± 11.3 [6]
Total plant sterol intake	—	52.0 ± 18.3	182.7 ± 62.8	24.9 ± 9.1	10.7 ± 5.4	14.7 ± 6.5	285.0 ± 96.7 [100]
Men	—	56.8 ± 19.5	195.8 ± 67.3	27.0 ± 9.7	11.6 ± 6.1	16.1 ± 7.3	307.3 ± 103.9
Women	—	47.3 ± 15.8	170.0 ± 55.3	22.6 ± 7.9	9.7 ± 4.5	13.3 ± 5.3	262.9 ± 83.7

[1] $\bar{x}$ ± SD; percentage contribution in brackets.

times in the follow-up period were assumed. Cases were thereby enumerated from the whole cohort of 120 852 subjects. Person-years at risk for each quintile of intake were estimated for the 3123 subjects of the subcohort. Rate ratios (RRs) and 95% CIs were calculated separately for each sex with the GLIM statistical package (28). Plant sterol intakes were entered into the models as quintiles of campesterol, β-sitosterol, stigmasterol, campestanol, and β-sitostanol intakes.

RRs for colon and rectal cancers were determined in 3 different multivariate analyses. In the first model, only age was adjusted for. The second model included the following confounding factors: age, smoking (pack-years, ie, the average number of packs of cigarettes smoked/d × the number of years smoked), alcohol use, family history of colorectal cancer, education level, and cholecystectomy. The third model included the same confounders as the second model, but an additional adjustment for energy was made. All confounding factors were included as categorical variables, except for age and energy, which were continuous. The etiology of gastrointestinal cancers depends on sex and the site of the cancer (29). Therefore, men and women and colon and rectal cancers were treated separately. Moreover, effects on different sites of the colon (ie, proximal and distal) were also estimated. Data analysis was performed with and without exclusion of the cases detected in the first year of follow-up. Because fat, meat, and calcium intakes were shown not to influence the risk of colorectal cancer in the Netherlands Cohort Study on Diet and Cancer, these variables were not included in the analyses as confounding factors (30, 31). Dietary fiber and vitamin E intakes were also not included because they are highly correlated with plant sterol intakes. This collinearity would have resulted in imprecise risk estimates that would have been difficult to interpret. Intakes are presented as means ± SDs.

RESULTS

The total intake of the 5 plant sterols in the subcohort was 307.3 ± 103.9 mg/d for men and 262.9 ± 83.7 mg/d for women (**Table 1**). Men had a 17% higher total intake than did women. The

TABLE 2
Pearson correlation coefficients between intakes of selected nutrients and plant sterols for 3123 men and women combined in the subcohort

Nutrient	Intake[1]	Campesterol[2]	β-Sitosterol[2]	Stigmasterol[2]	Campestanol[2]	β-Sitostanol[2]	Total[2]
Energy (kJ)	8117 ± 2176	0.68	0.61	0.63	0.38	0.47	0.64
Fat (g)							
Total	84 ± 28	0.66 (0.31)	0.59 (0.22)	0.63 (0.32)	0.30 (0.04)	0.59 (0.06)	0.61 (0.24)
Monounsaturated	31 ± 11	0.57 (0.14)	0.43 (−0.06)	0.52 (0.10)	0.18 (−0.15)	0.28 (−0.09)	0.46 (−0.02)
Polyunsaturated	17 ± 9	0.75 (0.63)	0.84 (0.76)	0.86 (0.80)	0.42 (0.29)	0.42 (0.25)	0.82 (0.74)
Linoleic acid	14 ± 8	0.69 (0.59)	0.82 (0.77)	0.82 (0.78)	0.42 (0.31)	0.40 (0.26)	0.80 (0.73)
Carbohydrate, total (g)	202 ± 63	0.61 (0.26)	0.53 (0.22)	0.54 (0.17)	0.42 (0.28)	0.51 (0.33)	0.59 (0.26)
Fiber (g)							
Total dietary	27 ± 8	0.73 (0.60)	0.78 (0.68)	0.68 (0.52)	0.76 (0.74)	0.81 (0.77)	0.80 (0.72)
Vegetable[3]	15 ± 5	0.45 (0.11)	0.57 (0.32)	0.56 (0.32)	0.23 (0.01)	0.30 (0.03)	0.54 (0.27)
Cereal	11 ± 5	0.70 (0.65)	0.66 (0.59)	0.49 (0.36)	0.97 (0.97)	0.98 (0.98)	0.72 (0.68)
β-Carotene (mg)	2.9 ± 1.5	0.28 (0.12)	0.32 (0.23)	0.36 (0.28)	0.18 (0.06)	0.22 (0.07)	0.32 (0.21)
Vitamin C (mg)	102 ± 44	0.24 (0.10)	0.41 (0.32)	0.29 (0.19)	0.13 (0.03)	0.14 (0.02)	0.36 (0.25)
Vitamin E (mg)	13 ± 6	0.73 (0.61)	0.84 (0.78)	0.84 (0.78)	0.42 (0.29)	0.42 (0.26)	0.82 (0.74)
Campesterol	—	1.00 (1.00)	—	—	—	—	—
β-Sitosterol	—	0.88 (0.81)	1.00 (1.00)	—	—	—	—
Stigmasterol	—	0.85 (0.74)	0.90 (0.85)	1.00 (1.00)	—	—	—
Campestanol	—	0.71 (0.67)	0.71 (0.66)	0.53 (0.43)	1.00 (1.00)	—	—
β-Sitostanol	—	0.76 (0.70)	0.72 (0.63)	0.57 (0.43)	0.98 (0.99)	1.00 (1.00)	—
Total sterols	—	0.93 (0.88)	0.99 (0.98)	0.91 (0.85)	0.76 (0.74)	0.79 (0.73)	1.00 (1.00)

[1] $\bar{x}$ ± SD.
[2] Energy-adjusted coefficients in parentheses.
[3] Includes dietary fiber from vegetables, legumes, fruit, nuts, and potatoes.

major plant sterol was β-sitosterol, representing 64% of the total intake of the 5 plant sterols, followed by campesterol (18%) and stigmasterol (9%). The plant stanols β-sitostanol and campestanol represented 5% and 4%, respectively, of the total intake. The main dietary sources of plant sterols were bread and vegetable fats (36% and 26% of the total plant sterol intake, respectively), especially breads with a high fiber content, such as brown bread and wholewheat bread, and margarines containing 80% fat. Worth mention was the low intake of plant sterols (≈2%) from vegetable oils, despite their high plant sterol concentration. There was a high intake of fruit and vegetables, which have low plant sterol concentrations, contributing 10% and 11% of plant sterols, respectively. Overall, it is important to emphasize that plant sterols were present in all food groups, whereas plant stanols came almost exclusively from high-fiber bread. This finding was further supported by the very high correlation coefficients between plant stanols and cereal fiber, which were close to 1, with or without adjustment for energy (**Table 2**). Non-energy-adjusted Pearson's correlation coefficients between total plant sterol intake and intake of polyunsaturated fat, linoleic acid, total dietary fiber, and vitamin E were high (>0.8), although they declined slightly after adjustment for energy (0.72–0.74). Correlation coefficients between energy and the sterols and stanols were intermediate.

The RRs and 95% CIs for colon and rectal cancers showed that results were not significantly different after the cases diagnosed during the first year of follow up were excluded; therefore, the results for the whole follow-up period are presented. Moreover, the results of the only age-adjusted model corresponded very well with the model after age, smoking (pack-years), alcohol use, family history of colorectal cancer, education level, and cholecystectomy were controlled for. One exception was the risk of colon cancer in men, which appeared to be negatively associated with high intakes of stigmasterol (RR: 0.68; 95% CI: 0.46, 0.99) in the highest quintile of intake in the age-adjusted model.

In men and women, there was no clear association between either plant sterol or stanol intake and colon cancer risk in either of the 2 presented models (**Table 3**). There were 2 exceptions to this in men: there was a positive association for energy-adjusted RRs for stigmasterol (P for trend = 0.03) and an inverse association for non-energy-adjusted risks for the stanols β-sitostanol (P for trend = 0.05) and campestanol (P for trend = 0.08). Colon cancer at proximal sites appeared to be somewhat positively associated with plant sterol intake, although only the association with stigmasterol intake in women was significant (**Table 4**). No association was found between plant sterol intake and colon cancer at distal sites in men and women, except for the nonsignificant inverse association for stigmasterol in women. Plant stanol intake was not associated with colon cancer at proximal sites. However, both plant stanols were positively associated with distal cancers in men, although only significantly so for β-sitostanol. Nonsignificant inverse associations were observed for plant stanols in women.

In men, there were positive associations between campesterol and stigmasterol intakes and rectal cancer in all models, but there was no association seen for β-sitosterol intake and plant stanol concentrations (**Table 5**). Except for β-sitostanol, plant sterol and stanol intakes tended to be inversely associated with rectal cancer in women, but the trend was not consistently linear.

DISCUSSION

To our knowledge this is the first prospective epidemiologic study of plant sterol and stanol intakes in relation to the risk of colorectal cancer. The estimated intake of β-sitosterol, campesterol, and stigmasterol of 259 mg/d in the Netherlands Cohort Study on Diet and Cancer was higher than the average per capita intake of 163 mg/d in the United Kingdom in 1991 (32). The plant stanol intake observed in the present study (26 mg/d) was comparable with the stigmasterol intake (25 mg/d), which was substantial considering that stanols are generally not included in

TABLE 3
Rate ratios (RRs) and 95% CIs for colon cancer in quintiles (Q) of plant sterol intake

	Men				Women			
	Intake	No. of cases	RR (CI) model 1[1]	RR (CI) model 2[2]	Intake	No. of cases	RR (CI) model 1[1]	RR (CI) model 2[2]
	mg/d				*mg/d*			
Campesterol								
Q1 (low)	34	65	1.00	1.00	30	63	1.00	1.00
Q2	45	59	0.98 (0.66, 1.46)	1.06 (0.71, 1.59)	38	61	1.01 (0.68, 1.52)	1.04 (0.69, 1.56)
Q3	54	68	1.06 (0.72, 1.55)	1.21 (0.80, 1.83)	45	52	0.87 (0.57, 1.31)	0.91 (0.59, 1.40)
Q4	64	55	0.91 (0.61, 1.37)	1.11 (0.71, 1.75)	53	49	0.81 (0.54, 1.24)	0.87 (0.54, 1.38)
Q5 (high)	81	56	0.96 (0.64, 1.44)	1.28 (0.77, 2.11)	68	46	0.81 (0.53, 1.24)	0.89 (0.52, 1.54)
P for trend	—	—	0.72	0.32	—	—	0.14	0.45
β-Sitosterol								
Q1 (low)	119	65	1.00	1.00	108	64	1.00	1.00
Q2	156	67	0.76 (0.51, 1.13)	1.20 (0.81, 1.78)	137	63	0.96 (0.65, 1.42)	0.98 (0.66, 1.46)
Q3	186	41	0.66 (0.44, 0.99)	0.69 (0.44, 1.08)	161	54	0.87 (0.58, 1.31)	0.90 (0.59, 1.38)
Q4	220	67	0.72 (0.48, 1.08)	1.28 (0.83, 1.96)	193	37	0.60 (0.39, 0.94)	0.63 (0.39, 1.05)
Q5 (high)	286	63	0.67 (0.45, 1.02)	1.38 (0.86, 2.21)	242	53	0.87 (0.58, 1.32)	0.95 (0.57, 1.59)
P for trend	—	—	0.15	0.16	—	—	0.10	0.32
Stigmasterol								
Q1 (low)	16	60	1.00	1.00	14	75	1.00	1.00
Q2	22	63	1.06 (0.71, 1.58)	1.18 (0.78, 1.77)	18	53	1.06 (0.71, 1.60)	0.73 (0.51, 1.14)
Q3	26	51	0.87 (0.57, 1.31)	1.01 (0.65, 1.56)	22	47	0.87 (0.57, 1.31)	0.67 (0.43, 1.02)
Q4	31	59	0.99 (0.66, 1.49)	1.25 (0.81, 1.94)	26	49	0.99 (0.66, 1.49)	0.73 (0.47, 1.15)
Q5 (high)	39	70	1.26 (0.85, 1.86)	1.84 (1.14, 2.96)	32	47	1.26 (0.85, 1.86)	0.70 (0.41, 1.17)
P for trend	—	—	0.32	0.03	—	—	0.32	0.11
Campestanol								
Q1 (low)	5	72	1.00	1.00	5	69	1.00	1.00
Q2	8	62	0.85 (0.58, 1.26)	0.87 (0.59, 1.28)	7	47	0.77 (0.51, 1.17)	0.79 (0.52, 1.21)
Q3	10	64	0.88 (0.60, 1.30)	0.93 (0.63, 1.37)	8	55	0.87 (0.58, 1.30)	0.91 (0.60, 1.37)
Q4	14	50	0.67 (0.45, 1.01)	0.71 (0.46, 1.07)	10	53	0.88 (0.58, 1.32)	0.92 (0.61, 1.40)
Q5 (high)	19	55	0.79 (0.53, 1.18)	0.86 (0.56, 1.31)	13	47	0.83 (0.55, 1.26)	0.91 (0.58, 1.43)
P for trend	—	—	0.08	0.22	—	—	0.52	0.87
β-Sitostanol								
Q1 (low)	8	69	1.00	1.00	7	65	1.00	1.00
Q2	12	72	1.05 (0.72, 1.53)	1.07 (0.73, 1.56)	10	45	0.78 (0.51, 1.19)	0.80 (0.52, 1.23)
Q3	15	61	0.88 (0.60, 1.30)	0.92 (0.62, 1.36)	13	61	1.04 (0.69, 1.54)	1.10 (0.73, 1.65)
Q4	19	46	0.64 (0.42, 0.98)	0.68 (0.44, 1.06)	15	52	0.91 (0.60, 1.38)	0.99 (0.64, 1.53)
Q5 (high)	25	55	0.85 (0.57, 1.27)	0.92 (0.60, 1.43)	20	48	0.89 (0.59, 1.37)	1.02 (0.64, 1.64)
P for trend	—	—	0.05	0.18	—	—	0.84	0.62

[1] Adjusted for age, smoking (pack-years), alcohol use, family history of colorectal cancer, education level, and cholecystectomy.
[2] Adjusted for age, smoking (pack-years), alcohol use, family history of colorectal cancer, education level, cholecystectomy, and energy intake.

dietary analyses because of their low concentrations in many foods. Different dietary assessment and analytic methods complicate comparisons between countries, but studies performed in countries with different food cultures indicate that variations in food patterns influence total intakes because plant sterols exist in many foods.

Introduction of one plant-sterol-rich source into the diet might not increase the sterol content of the diet considerably; however, overall consumption of foods rich in unsaturated fat and dietary fiber would result in a high intake of plant sterols. This is exemplified by the estimated intake of β-sitosterol and stigmasterol in the general American population (78 mg/d) relative to that in lactoovovegetarian Seventh-day Adventists (344 mg/d) in 1984 (5). This high intake in the Seventh-day Adventists is similar to the per capita combined intake of β-sitosterol, campesterol, stigmasterol, and brassicasterol in Japan in 1987 (33). Moreover, 372 semiacculturated Tarahumara Indians in the Sierra Madre, Mexico, who consumed a diet based on staple foods like corn and beans, also had a total intake of ≈400 mg plant sterols/d (34). In general, it seems that the highest documented plant sterol intakes are not typically found in westernized cultures.

Bread was one important source of all plant sterols in the Netherlands, and the common Dutch habit of eating brown bread for breakfast and lunch might have resulted in a higher intake of sterols than observed in the United Kingdom. The finding that cereal products were important sources of plant sterol intakes in both of these countries is of interest considering the former focus on vegetable oils as important sources because of their high concentrations of plant sterols (1). The present study showed that not only the consumption of foods with a high sterol concentration but also the relatively high consumption of several food groups with a relatively low concentration was an important contributor to plant sterol intakes. For example, a high consumption of fruit and vegetables—which seldom have a concentration

TABLE 4
Rate ratios (RRs) and 95% CIs for colon cancer in quintiles (Q) of plant sterol intake for proximal and distal colon[1]

	Men		Women	
	Proximal (n = 140 cases)	Distal (n = 153 cases)	Proximal (n = 137 cases)	Distal (n = 121 cases)
Campesterol				
Q1 (low)	1.00	1.00	1.00	1.00
Q2	0.99 (0.58, 1.68)	1.04 (0.61, 1.76)	1.09 (0.63, 1.88)	1.25 (0.72, 2.16)
Q3	1.20 (0.70, 2.05)	1.01 (0.58, 1.77)	1.31 (0.75, 2.28)	0.95 (0.51, 1.75)
Q4	0.89 (0.48, 1.64)	0.93 (0.51, 1.70)	1.35 (0.74, 2.45)	0.96 (0.50, 1.84)
Q5 (high)	1.14 (0.59, 2.21)	1.05 (0.52, 2.13)	1.33 (0.67, 2.62)	1.06 (0.50, 2.26)
P for trend	0.84	0.94	0.28	0.82
β-Sitosterol				
Q1 (low)	1.00	1.00	1.00	1.00
Q2	1.22 (0.73, 2.03)	0.87 (0.51, 1.48)	1.20 (0.70, 2.06)	1.30 (0.76, 2.22)
Q3	0.51 (0.27, 0.97)	0.96 (0.55, 1.65)	0.88 (0.49, 1.58)	0.98 (0.54, 1.76)
Q4	1.15 (0.65, 2.03)	0.81 (0.43, 1.49)	1.49 (0.84, 2.64)	0.50 (0.24, 1.04)
Q5 (high)	1.27 (0.69, 2.35)	1.14 (0.60, 2.20)	1.59 (0.84, 3.01)	0.96 (0.47, 1.97)
P for trend	0.56	0.83	0.10	0.22
Stigmasterol				
Q1 (low)	1.00	1.00	1.00	1.00
Q2	1.11 (0.64, 1.90)	0.94 (0.56, 1.59)	1.38 (0.80, 2.37)	0.64 (0.37, 1.10)
Q3	0.98 (0.55, 1.74)	0.77 (0.44, 1.36)	1.14 (0.64, 2.06)	0.60 (0.34, 1.07)
Q4	1.18 (0.67, 2.11)	0.97 (0.54, 1.74)	1.36 (0.75, 2.50)	0.60 (0.33, 1.10)
Q5 (high)	1.56 (0.83, 2.95)	0.97 (0.50, 1.90)	2.52 (1.34, 4.75)	0.60 (0.30, 1.21)
P for trend	0.21	0.91	0.01	0.11
Campestanol				
Q1 (low)	1.00	1.00	1.00	1.00
Q2	0.67 (0.40, 1.14)	1.20 (0.70, 2.07)	1.20 (0.72, 1.98)	0.58 (0.33, 1.02)
Q3	1.00 (0.61, 1.64)	1.06 (0.60, 1.89)	0.87 (0.50, 1.50)	0.83 (0.49, 1.40)
Q4	0.52 (0.29, 0.93)	1.39 (0.80, 2.43)	0.97 (0.57, 1.67)	0.60 (0.34, 1.07)
Q5 (high)	0.90 (0.53, 1.54)	1.54 (0.86, 2.77)	0.86 (0.48, 1.55)	0.58 (0.31, 1.08)
P for trend	0.44	0.12	0.42	0.10
β-Sitostanol				
Q1 (low)	1.00	1.00	1.00	1.00
Q2	1.13 (0.68, 1.89)	1.21 (0.69, 2.11)	1.16 (0.71, 1.90)	0.51 (0.28, 0.93)
Q3	1.05 (0.62, 1.79)	1.26 (0.71, 2.25)	0.81 (0.47, 1.38)	1.02 (0.62, 1.69)
Q4	0.63 (0.35, 1.16)	1.61 (0.91, 2.83)	0.78 (0.44, 1.37)	0.55 (0.30, 1.02)
Q5 (high)	1.12 (0.64, 1.99)	1.83 (1.00, 3.37)	0.82 (0.45, 1.47)	0.59 (0.31, 1.13)
P for trend	0.62	0.03	0.19	0.14

[1] Rate ratios were adjusted for age, smoking (pack-years), alcohol use, family history of colorectal cancer, education level, cholecystectomy, and energy intake.

>20–30 mg per 100 g edible product (26)—contributed substantially to total sterol intakes.

Another interesting aspect of the finding that fiber-rich bread is an important source of plant sterols is the possibility that plant sterols are a confounding factor in statistical analyses of the association between colorectal cancer and dietary fiber intakes in epidemiologic studies. Because of the high correlation between sterols and dietary fiber, it is difficult to determine which substances are responsible for the association.

Both increased or decreased risks of colorectal cancer associated with different sources of fiber intake (eg, vegetables, fruit, and cereal) or no associations were described in previous cohort studies (35–39). Whether the conflicting results were due to variations in plant sterol intakes has not been investigated. However, a high correlation between dietary fiber and plant sterol intakes complicates the separation of the effects of both variables.

In the present study, one of the original aims of the Netherlands Cohort Study on Diet and Cancer—to study total fat intake, fat quality, and dietary fiber intake—was extended to include plant sterol intakes. Prospective, large-scale population studies are very expensive and time consuming, which makes it attractive to use the dietary data for another purpose. Therefore, interest in bioactive substances such as plant sterols, but also flavonoids and phytoestrogens, raises important issues concerning dietary assessments when methods originally designed for another purpose are used. The use of nonvalidated databases based on the use of different analytic methods appears to be one of the major problems. In the present study, a special effort was made to fit the questionnaire with analyzed plant sterol concentrations by using one method only, which increases the probability of high validity. A factor that is not so easily controlled is the variation over time in the composition of certain food items, such as margarines. For example, the price of oils at a given time determines to some extent the type of oil used in the production of margarine. This variation in composition and its effect on plant sterol concentrations of certain foods was not taken into account in the pres-

TABLE 5
Rate ratios (RRs) and 95% CIs for rectal cancer in quintiles (Q) of plant sterol intake

	Men				Women			
	Intake	No. of cases	RR (CI) model 1[1]	RR (CI) model 2[2]	Intake	No. of cases	RR (CI) model 1[1]	RR (CI) model 2[2]
	mg/d				*mg/d*			
Campesterol								
Q1 (low)	34	34	1.00	1.00	30	21	1.00	1.00
Q2	45	40	1.27 (0.78, 2.08)	1.37 (0.83, 2.27)	38	23	1.12 (0.60, 2.07)	1.11 (0.59, 2.08)
Q3	54	48	1.50 (0.93, 2.42)	1.72 (1.03, 2.86)	45	35	1.71 (0.97, 3.02)	1.69 (0.92, 3.09)
Q4	64	35	1.10 (0.66, 1.82)	1.33 (0.76, 2.34)	53	26	1.26 (0.69, 2.30)	1.23 (0.62, 2.44)
Q5 (high)	81	44	1.46 (0.90, 2.38)	1.92 (1.05, 3.53)	68	11	0.54 (0.25, 1.15)	0.52 (0.21, 1.29)
P for trend	—	—	0.23	0.06	—	—	0.31	0.52
β-Sitosterol								
Q1 (low)	119	39	1.00	1.00	108	19	1.00	1.00
Q2	156	36	0.99 (0.60, 1.61)	1.03 (0.63, 1.69)	137	29	1.43 (0.79, 2.63)	1.42 (0.77, 2.62)
Q3	186	43	1.09 (0.68, 1.74)	1.17 (0.71, 1.92)	161	32	1.64 (0.90, 2.97)	1.60 (0.86, 2.97)
Q4	220	45	1.20 (0.75, 1.91)	1.33 (0.79, 2.22)	193	25	1.31 (0.70, 2.45)	1.26 (0.62, 2.53)
Q5 (high)	286	38	1.06 (0.65, 1.73)	1.22 (0.69, 2.17)	242	11	0.57 (0.27, 1.23)	0.54 (0.22, 1.31)
P for trend	—	—	0.52	0.27	—	—	0.20	0.33
Stigmasterol								
Q1 (low)	16	38	1.00	1.00	14	24	1.00	1.00
Q2	22	34	0.91 (0.56, 1.50)	0.97 (0.59, 1.62)	18	25	1.04 (0.58, 1.87)	1.05 (0.58, 1.90)
Q3	26	43	1.16 (0.72, 1.86)	1.28 (0.78, 2.09)	22	24	1.00 (0.55, 1.80)	1.01 (0.54, 1.88)
Q4	31	38	1.00 (0.62, 1.63)	1.16 (0.69, 1.95)	26	27	1.14 (0.64, 2.03)	1.16 (0.61, 2.20)
Q5 (high)	39	48	1.32 (0.83, 2.12)	1.68 (0.96, 2.96)	32	16	0.68 (0.35, 1.32)	0.71 (0.2, 1.57)
P for trend	—	—	0.18	0.05	—	—	0.40	0.67
Campestanol								
Q1 (low)	5	43	1.00	1.00	5	27	1.00	1.00
Q2	8	36	0.85 (0.53, 1.37)	0.85 (0.53, 1.38)	7	20	0.81 (0.44, 1.48)	0.81 (0.44, 1.49)
Q3	10	38	0.90 (0.56, 1.44)	0.93 (0.57, 1.50)	8	33	1.25 (0.73, 2.15)	1.26 (0.73, 2.20)
Q4	14	37	0.90 (0.56, 1.46)	0.94 (0.58, 1.52)	10	24	0.93 (0.51, 1.67)	0.94 (0.51, 1.72)
Q5 (high)	19	47	1.20 (0.76, 1.90)	1.27 (0.79, 2.05)	13	12	0.49 (0.24, 1.00)	0.51 (0.24, 1.07)
P for trend	—	—	0.37	0.27	—	—	0.15	0.22
β-Sitostanol								
Q1 (low)	8	42	1.00	1.00	7	21	1.00	1.00
Q2	12	33	0.81 (0.50, 1.32)	0.82 (0.50, 1.35)	10	30	1.52 (0.85, 2.74)	1.54 (0.85, 2.77)
Q3	15	48	1.18 (0.75, 1.85)	1.22 (0.77, 1.94)	13	28	1.36 (0.75, 2.47)	1.37 (0.74, 2.52)
Q4	19	31	0.76 (0.46, 1.26)	0.81 (0.48, 1.36)	15	25	1.23 (0.66, 2.27)	1.24 (0.65, 2.37)
Q5 (high)	25	47	1.25 (0.79, 1.98)	1.36 (0.83, 2.24)	20	12	0.63 (0.30, 1.32)	0.65 (0.29, 1.44)
P for trend	—	—	0.38	0.24	—	—	0.21	0.32

[1] Adjusted for age, smoking (pack-years), alcohol use, family history of colorectal cancer, education level, and cholecystectomy.
[2] Adjusted for age, smoking (pack-years), alcohol use, family history of colorectal cancer, education level, cholecystectomy, and energy intake.

ent study because of a lack of information on changes in the brands of products used over the time period studied.

In most experimental studies of the relation between colorectal cancer risk and plant sterol intakes, β-sitosterol was the sterol used and the doses were 10-fold those of usual dietary doses (14–16). It might be argued that a mean intake of 183 mg β-sitosterol/d is too low to show a preventive effect. The observed positive associations were unexpected considering the many experimental studies in animals that showed a preventive effect of sterol intake; however, such positive associations were shown previously. A case-control study also described positive associations between campesterol and stigmasterol intakes and prostate cancer (40). In contrast, lung cancer was inversely associated with higher intakes of plant sterols in a case-control study (41). Campesterol, stigmasterol, campestanol, and β-sitostanol intakes have not been studied experimentally to the same extent as has β-sitosterol intake; therefore, it is difficult to draw any firm conclusions from these positive associations.

The higher risk of colorectal cancer associated with higher intakes of campesterol and stigmasterol observed among men in this study do not necessarily mean that these sterols alone have an unfavorable effect on large-bowel cancer, but that the effect may also depend on intakes of other plant sterols or bioactive substances in the diet that co-exist with the ones being studied. An alternative explanation is that plant sterols inhibit cholesterol absorption. A high intake of cholesterol has been suggested to be associated with an increased risk of colorectal cancer (42, 43). Plant sterols inhibit cholesterol absorption and thereby increase the excretion of cholesterol into the large bowel (13, 44). Because plant sterols are important bioactive substances currently used to lower serum cholesterol in a more efficient way than common dietary means, and mainly exert their effects without being absorbed, the physiologic implications for the human colon and rectum need to be established. In conclusion, a high dietary intake of plant sterols was not associated with a lower risk of colon and rectal cancers in the Netherlands Cohort Study on Diet and Cancer.

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