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Plant Sterols and Risk of Stomach Cancer: A Case-Control Study in Uruguay

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Abstract: *In 1997–1999, 120 incident and histologically verified cases of stomach cancer were frequency matched on age, gender, residence, and urban/rural status with 360 controls to study the role of diet in gastric cancer in Uruguay. We focused on the role of plant sterols (β-sitosterol, campesterol, stigmasterol, and total plant sterols) after controlling for major confounders. Total phytosterols were associated with a strong inverse relationship with stomach cancer (odds ratio of stomach cancer for total phytosterol intake in the highest tertile = 0.33, 95% confidence interval = 0.17–0.65). Joint exposure to high intake of total phytosterol and* a*-carotene was also inversely associated with gastric cancer risk (odds ratio = 0.09, 95% confidence interval = 0.02–0.32). High intake of total plant sterols explained most of the attenuation in risk of gastric cancer associated with vegetable and fruit intakes.*

Introduction

Stomach cancer is the third most frequently occurring cancer in the Uruguayan population, with age-adjusted incidence rates of 19.3 and 9.3 per 100,000 for men and women, respectively (1). More importantly, incidence rates in the northern region of Uruguay are much higher and comparable to those in many developing countries (34.8 and 29.9 per 100,000 for men and women, respectively) (2).

A diet rich in starch and salt and poor in vegetables and fruits has been associated with increased risks of stomach cancer (3–5). Vegetables and fruits are rich in several groups of micronutrients, particularly carotenoids, vitamin C, flavonoids, and phytosterols. The latter compounds (i.e., plant sterols) have been suggested as anticarcinogenic in experimental studies on colon and prostate cancer (6,7). Phytosterols are structurally similar to cholesterol, except they always contain substitutions at the C-24 position of the sterol side chain (8). To our knowledge, there are no epidemiological studies on plant sterols and gastric cancer, mostly because of the lack of an adequate database. Recently, Pillow and co-workers (9) published a database on phytoestrogens, including information on plant sterols. According to this database, fruits contribute 36.4% of the total phytosterol intake in Uruguay, followed by vegetables (15.9%) and tubers (11.3%). Therefore, we considered that a study with detailed information about plant sterols would contribute important new information about the role of fruits and vegetables in protection from cancer. For this reason, we have conducted a case-control study on plant sterols and gastric cancer risk.

Subjects and Methods

Between September 1997 and August 1999, a case-control study on diet and stomach cancer was carried out in Uruguay. All newly diagnosed and histologically verified cases with gastric cancer were considered eligible for the study. One hundred twenty-eight cases of stomach cancer were diagnosed in the four major hospitals of Montevideo. Of this initial number, eight patients were too ill, and the interview with them was not possible. Thus 120 patients with stomach cancer were included in the study (response rate 93.7%).

Controls were selected from the same hospitals as the cases, over the same time period. A total of 372 patients with nonneoplastic diseases were considered eligible. From this initial number, 12 patients refused the interview, leading to a final number of 360 patients (response rate 96.7%). These controls were frequency matched to the cases on age (10-yr intervals), gender, residence (Montevideo and the rest of the country), and urban/rural status. The diagnostic categories among controls were eye disorders (95 patients, 26.4%), abdominal hernia (76, 21.1%), acute appendicitis (52, 14.4%), fractures and injuries (41, 11.4%), skin diseases (38, 10.7%), varicose veins (24, 6.6%), hydatid cyst (19, 5.3%), and anemia (15, 4.1%).

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Cases and controls were interviewed face-to-face in the hospitals shortly after admittance by two trained social workers. The questionnaire included the following sections: 1) sociodemographic characteristics, 2) a complete history of tobacco smoking, 3) a complete section on alcohol drinking, 4) a complete history of "mate" drinking (a local herb tea), 5) a complete occupational history, based on job titles, 6) history of cancer in first-degree relatives, and 7) a food frequency questionnaire on 64 items. Dietary information was requested from the cases five years before onset of the gastric symptoms and from controls five years before the interview. Moreover, the consumption of salted meat between 10 and 15 years of age was ascertained and was correlated with consumption five years before the onset of symptoms. The Pearson correlation coefficients were 0.49 for cases and 0.44 for controls, suggesting that recall of adolescent diet was moderately reliable.

The food frequency questionnaire allowed the calculation of total energy intake and has been previously tested for reproducibility. According to this study, Pearson correlation cofficients ranged from 0.30 for calcium to 0.83 for saturated fat.

Food items were recorded as continuous variables by multiplying the portion size of a middle-aged adult by the times of consumption (per day, week, or month). Nutrients were calculated using local food tables (10) and categorized in tertiles according to the distribution of the sample of controls. In the case of plant sterols, there were no national values, and we employed the tables developed by Pillow and co-workers (9). These authors developed a new database on phytoestrogens, including plant sterols, based on literature information, including amount per 100 g for each food containing phytosterols. Nutrients were adjusted for total energy intake by the residuals method (11).

Odds ratios (ORs) were calculated by unconditional logistic regression, after the terms for frequency matching (age, gender, residence, and urban/rural status) were included in the initial model (12). ORs for each phytosterol were calculated for gender, and the results showed no heterogeneity. Therefore, all subsequent analyses were calculated for both genders combined after a term for gender was included in the model. Potential confounders were included in more complex models. Among them, body mass index, family history of gastric cancer, and total energy intake were included in all models. Moreover, the contribution of phytosterols to the effect of vegetable and fruit intake was addressed in a model that included a term for these food groups and a term for each plant sterol. All the calculations were performed with the STATA statistical package (13).

Results

The distribution of cases and controls among sociodemographic and other variables is shown in Table 1. As a result of the matched design, distribution of age, gender, residence, and urban/rural status was similar among cases and controls. Cases were less educated and consumed more energy than controls.

ORs of stomach cancer for plant sterols are shown in Table 2. β-Sitosterol intake was inversely associated with stomach cancer risk. The OR for those patients consuming high levels of β-sitosterol (>56.0 mg/day) compared with subjects in the lowest tertile (<30.2 mg/day) was 0.34 [95% confidence interval (CI) = 0.15–0.76] after total energy, legume, starch, vitamin C, and α-carotene intakes were controlled. High campesterol intake showed an OR of 0.90 (95% CI = 0.45–1.82), whereas stigmasterol intake displayed an inverse association with gastric cancer (OR = 0.51, 95% CI = 0.25–1.06). Finally, high total phytosterol intake (>82.5 mg/day) was associated with an inverse relationship with gastric cancer risk [OR = 0.33, 95% CI = 0.15–0.75, p (for trend) = 0.01].

ORs of stomach cancer for vegetable intake, after plant sterols were controlled, are shown in Table 3. Vegetable intake was associated with an inverse relationship after total sterol intake was controlled (OR = 0.77, 95% CI = 0.42–1.41). This association was substantially minor compared with that shown by vegetable intake without control for plant sterols (OR = 0.56, 95% CI = 0.31–0.98).

ORs of gastric cancer for high total fruit intake showed an inverse association of 0.44 (95% CI = 0.25–0.77; Table 4). When fruit intake was further adjusted for total sterols, this association was attenuated (OR = 0.75, 95% CI = 0.38–1.49). These results suggest that the phytosterol content of fruits and vegetables may be responsible for the observed effect. Joint effect of β-sitosterol and α-carotene showed a strong inverse association with stomach cancer (OR = 0.09, 95% CI = 0.02–0.32). Both micronutrients displayed independent effects (Table 5). Because 35.5% of the controls were afflicted by abdominal hernia and acute appendicitis, we performed a separate analysis in which we compared cases with other controls and cases with patients suffering from gastrointestinal diseases, and the results were similar (results not shown).

Discussion

According to our results, plant sterols were inversely associated with risk of stomach cancer. This association was strong and statistically significant and showed a dose-response effect [p (for trend) = 0.01]. Moreover, this inverse association remained after control for vegetables, fruits, legumes, starch, salt, and other nutrients. Previous studies on gastric cancer and vegetable and fruit intake (main source of plant sterols) have shown a consistent protective effect exerted by these foods (3,14–20).

Plant sterols have shown an anticarcinogenic effect against colon and prostate cancer in experimental studies (7,21–25). To our knowledge, only one epidemiological study on plant sterols and cancer has been performed. In this study, Mendilaharsu and co-workers (26) reported an inverse association between phytosterols and lung cancer risk.

Table 1. Distribution of Cases and Controls by Sociodemographic Characteristics and Selected Risk Factors[a]

Variable	Cases (n = 120)	Controls (n = 360)	P Value
Age, yr			
30–39	3 (2.5)	9 (2.5)	
40–49	5 (4.2)	15 (4.2)	
50–59	30 (25.0)	90 (25.0)	
60–69	33 (27.5)	99 (27.5)	
70–79	42 (35.0)	126 (35.0)	
80–89	7 (5.8)	21 (5.8)	1.00
Gender			
Male	85 (70.8)	255 (70.8)	
Female	35 (29.2)	105 (29.2)	1.00
Residence			
Montevideo	70 (58.3)	210 (58.3)	
Other counties	50 (41.7)	150 (41.7)	1.00
Urban/rural status			
Urban	96 (80.0)	290 (80.6)	
Rural	24 (20.0)	70 (19.4)	1.00
Education, yr			
0–4	71 (59.2)	177 (49.2)	
≥5	49 (40.8)	183 (50.8)	0.08
Monthly income, US dollars			
≤154	47 (39.2)	135 (37.5)	
≥155	47 (39.2)	122 (33.9)	
Unknown	26 (21.7)	103 (28.6)	0.29
Body mass index			
≤24.1	50 (41.7)	120 (33.3)	
24.2–27.2	35 (29.2)	118 (32.8)	
≥27.3	35 (29.2)	122 (33.9)	0.25
Family history of gastric cancer			
No	114 (95.0)	348 (96.7)	
Yes	6 (5.0)	12 (3.3)	0.57
Total energy intake			
Low	17 (14.2)	120 (33.3)	
Medium	43 (35.8)	120 (33.3)	
High	60 (50.0)	120 (33.3)	<0.001

a: Values in parentheses are percentages.

It has been suggested that plant sterols could induce decreased cell growth and apoptosis through ceramide production (21–23). This is a direct effect of the plant sterols in the sphingomyelin cycle. Also, ergosterol has shown antioxidant properties (27). More specifically, the ergosterol-containing lipid fraction derived from yeast microsomal membranes inhibited lipid peroxidation when introduced into ox brain phospholipid liposomes. Finally, phytosterols compete with cell receptors in the large bowel, with the resulting decreased absorption of cholesterol (6,28,29). This appears to be of less importance, since cholesterol has not been recognized as a risk factor for gastric cancer (5). It is not possible to exclude the possibility that plant sterols are markers of other unknown chemicals in vegetables and fruits. In this sense, these plant foods are extremely rich in dietary antioxidants and other substances.

The present study has several potential limitations. First, the possibility of differential reporting bias is difficult to rule out. We have tried to minimize this important problem by asking the cases about their diet five years before the onset of symptoms and the controls about their diet five years before the interview. Second, recall bias is almost impossible to rule out, as in all case-control studies. Against this possibility, it should be mentioned that our study population (cases and controls) comes mainly from low socioeconomic strata, with scanty information on the role of diet and stomach cancer. Also, compared with population-based controls, hospitalized controls are more similar to cases with regard to recall accuracy. As in most studies, errors in the measurements of the dietary intake are almost certain. Nevertheless, this misclassification bias is likely to be nondifferential, leading the ORs to the null. Therefore, this measurement error is of less importance when an effect is detected, as happened in our study. Finally, we were unable to control for *Helicobacter pylori* infection, since our patients were not examined with laboratory techniques for detection of this infection. We tried to minimize this problem by adjusting for education, since *H. pylori* infection is more prevalent among patients with low incomes. After this adjustment, the results remained unchanged.

On the other hand, the study has several strengths, namely, the high response rate for cases and controls and the absence of proxy responses.

Table 2. ORs of Stomach Cancer for Phytosterol Intake[a]

Phytosterol	Cases/ Controls	OR	95% CI
β-Sitosterol, mg/day			
≤30.1	65/120	1.0	
30.2–56.0	39/120	0.71	0.39–1.30
≥56.1	16/120	0.34	0.15–0.76
p (for trend) = 0.01			
Campesterol, mg/day			
≤7.1	63/120	1.0	
7.2–13.6	30/120	0.72	0.40–1.29
≥13.7	27/120	0.90	0.45–1.82
p (for trend) = 0.67			
Stigmasterol, mg/day			
≤5.8	65/120	1.0	
5.9–9.1	33/120	0.65	0.37–1.16
≥9.2	22/120	0.51	0.25–1.06
p (for trend) = 0.06			
Total phytosterols, mg/day			
≤45.5	65/120	1.0	
45.6–82.5	39/120	0.73	0.40–1.33
≥82.6	16/120	0.33	0.15–0.75
p (for trend) = 0.01			

a: Adjusted for age, gender, residence, urban/rural status, education, body mass index, and total energy, legume, starch, vitamin C, and α-carotene intakes. OR, odds ratio; CI, confidence interval.

Table 3. ORs of Stomach Cancer for Vegetable Intake, After Controlling for Phytosterol Intake[a,b]

	Tertiles		
Confounder	I	II	III
None	1.0	1.07 (0.65–1.79)	0.56 (0.31–0.98)
β-Sitosterol	1.0	1.21 (0.71–2.04)	0.79 (0.43–1.44)
Campesterol	1.0	1.17 (0.70–1.96)	0.74 (0.41–1.36)
Stigmasterol	1.0	1.23 (0.73–2.08)	0.83 (0.44–1.54)
Total sterols	1.0	1.21 (0.72–2.06)	0.77 (0.42–1.41)

a: Adjusted for age, gender, residence, urban/rural status, education, body mass index, and total energy and for each plant sterol.
b: Values in parentheses are 95% CIs.

Table 4. ORs of Stomach Cancer for Fruit Intake, After Controlling for Plant Sterols[a,b]

	Tertiles		
Confounder	I	II	III
None	1.0	0.73 (0.45–1.19)	0.44 (0.25–0.77)
β-Sitosterol	1.0	0.87 (0.50–1.51)	0.77 (0.39–1.54)
Campesterol	1.0	0.80 (0.46–1.40)	0.62 (0.31–1.21)
Stigmasterol	1.0	0.81 (0.47–1.40)	0.69 (0.35–1.34)
Total sterols	1.0	0.87 (0.50–1.51)	0.75 (0.38–1.49)

a: Adjusted for age, gender, residence, urban/rural status, education, body mass index, and total energy and for each plant sterol.
b: Values in parentheses are 95% CIs.

Table 5. Joint Effect of Intake of β-Sitosterol and α-Carotene on Gastric Cancer Risk[a,b]

	α-Carotene		
	Low	Medium	High
β-Sitosterol			
Low	1.0[c]	0.6 (0.2–1.4)	0.4 (0.1–0.9)
Medium	0.8 (0.4–1.7)	0.4 (0.2–0.9)	0.2 (0.1–0.5)
High	0.4 (0.1–1.0)	0.2 (0.1–0.5)	0.1 (0.02–0.3)
	1.0[d]	0.6 (0.4–1.0)	0.3 (0.2–0.6)

	1.0[d]
	0.7 (0.4–1.2)
	0.3 (0.1–0.6)

a: Adjusted for age, gender, residence, urban/rural status, education, family history, body mass index, and total energy intake and for each other.
b: Values in parentheses are 95% CIs.
c: Reference category for analysis of joint effects.
d: Reference category for analysis of marginal effects.

In summary, the present study is the first to show an inverse association between phytosterols, more specifically β-sitosterol and stigmasterol, and stomach cancer risk. The relationship remains after control for other antioxidants, such as vitamin C. This inverse association can be interpreted to suggest a protective effect of phytosterols against stomach cancer. This effect of plant sterols could have a major public health impact in a disease such as gastric cancer, which presents a high incidence and a poor prognosis.

Acknowledgments and Notes

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