

### Short Communication

## $\alpha$ -Linolenic Acid and Risk of Prostate Cancer: A Case-Control Study in Uruguay<sup>1</sup>

Eduardo De Stéfani,<sup>2</sup> Hugo Deneo-Pellegrini, Paolo Boffetta, Alvaro Ronco, and María Mendilaharsu

Registro Nacional de Cáncer, 11300 Montevideo, Uruguay [E. D. S., H. D.-P., A. R., M. M.], and Unit of Environmental Cancer Epidemiology, International Agency for Research on Cancer, 69372 Lyon, France [P. B.]

#### Abstract

In the time period of 1994–1998, a case-control study on diet and prostate cancer was carried out in Uruguay to examine the risk associated with fat intake. Two hundred and seventeen (217) incident cases afflicted with advanced prostate cancer were frequency-matched with 431 controls on age, residence, and urban/rural status. The analysis was carried out using unconditional multiple logistic regression.  $\alpha$ -Linolenic acid was associated with a strong positive association (fourth quartile of intake odds ratio, 3.91; 95% confidence interval, 1.50–10.1) after controlling for total calorie intake and for the other types of fat. The effect was similar when  $\alpha$ -linolenic acid was analyzed by its sources of origin (odds ratio for vegetable linolenic acid, 2.03; 95% confidence interval, 1.01–4.07). Including this report, five of six studies that have examined the relationship between  $\alpha$ -linolenic acid and prostate cancer yielded a positive association, which was significant in four studies. Thus, there appears to be evidence of a role of  $\alpha$ -linolenic acid in prostate carcinogenesis.

#### Introduction

Prostate cancer is the second most common malignancy among Uruguayan men after lung cancer, with an age-adjusted incidence rate of 35.2 per 100,000 for the years 1990–1992 (1). The reasons for this high frequency are unknown. Recently, Giovannucci *et al.* (2) reported a positive association between  $\alpha$ -linolenic acid, one of the essential fatty acids, and prostate cancer. The main sources of linolenic acid in the Giovannucci *et al.* (2) study were mayonnaise, margarine, butter, and beef. Among male patients included as controls in previous case-control studies, the main source of  $\alpha$ -linolenic acid in Uruguay was red meat (53.8%), followed by dairy foods (18.0%), vegetables (10.7%), and processed meats (7.8%; Ref. 3). Because

red meat consumption in Uruguay is one of the highest in the world (219.4 g/day), and meat intake has been implicated as a risk factor for prostate cancer, its importance as a source of  $\alpha$ -linolenic acid in the Uruguayan diet is evident. Fat intake has been associated with an increased risk of prostate cancer in most, but not all, studies dealing with this malignancy (4). For these reasons, we decided to investigate the role of  $\alpha$ -linolenic acid in the etiology of prostate cancer.

#### Subjects and Methods

In the period of 1994–1998, all patients newly diagnosed with advanced prostate cancer in the four major hospitals of Montevideo, Uruguay were considered eligible for this study. In this period, 234 patients with advanced prostate cancer were ascertained. Seventeen (17) patients refused to be interviewed, leading to a final total of 217 cases (response rate, 92.7%). All patients with prostate cancer were diagnosed by histological examination of biopsies, transurethral resection specimens, and/or prostatectomies. Thirty five percent (35%) of the patients were diagnosed several months (mean time, 6 months) before hospitalization, and the mean time of the interview after diagnosis was 45 months. For the purpose of the present study, advanced prostate cancer was defined as prostate cancer with regional or disseminated disease. According to the staging rules of the International Union against Cancer (5), tumors >1.5 cm that invaded the capsule or tumors with regional metastasis were considered as advanced tumors. The proportion of regional cases was of 72.7%, whereas 27.3% were patients with local disseminated disease. All cases were verified histologically as adenocarcinomas and occurred in white patients. Furthermore, all of the cases were initially diagnosed in the hospitals, and there were no referrals from other centers.

In the same period, 445 patients afflicted with diseases not related with the digestive and urinary tracts were eligible for this study. Fourteen (14) patients refused the interview (response rate, 96.8%), leading to a final number of 431 patients. The most frequent disease categories among controls were eye disorders (146 patients, 33.9%), abdominal hernia (113 patients, 26.2%), fractures (42 patients, 9.7%), acute appendicitis (36 patients, 8.4%), osteoarticular disorders (32 patients, 7.4%), varicose veins (26 patients, 6.1%), hydatid cyst (19 patients, 4.4%), and anemia (17 patients, 3.9%). Controls were frequency-matched to cases on age (5-year interval), residence (Montevideo, other counties), and urban/rural status. All patients were whites. Both cases and controls were submitted to a detailed interview shortly after admission into the hospital. The questionnaire included sections on demography, occupation, tobacco smoking, alcohol drinking, “mate” drinking, sexual activity (age at first intercourse, number of children, annual number of intercourses, number of sexual partners, and number of sexually transmitted diseases). Finally, the interview in-

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<sup>2</sup> To whom requests for reprints should be addressed, at Registro Nacional de Departmento Cáncer, Avda. Brasil 3080 dep. 402, Montevideo, Uruguay. Fax: 598-2-402-08-10.

cluded an FFQ<sup>3</sup> on 64 food items. This FFQ was previously tested for repeatability (3). In brief, 80 male healthy volunteers were face-to-face interviewed with this questionnaire. Eight months later, they were submitted to the same questionnaire, and the resulting correlation coefficients between both interviews were calculated. The results presented ranged from 0.31 for calcium and 0.87 for saturated fat. In the opinion of the authors, the FFQ accurately represented the food consumption pattern of the Uruguayan population. Total fat, saturated fat, and monounsaturated fat were highly correlated in the repeatability study. Correlation coefficients between total fat and saturated fat were 0.87, whereas the correlation coefficient between total fat and monounsaturated fat was 0.81. For the purposes of the study, fatty food items were grouped as follows: beef, red meat, white meat (chicken and fish), processed meat, offal, dairy foods, desserts, and eggs. Furthermore, the food groups were divided into quartiles, following the 25, 50, and 75 percentiles of the sample of controls. Nutrients were calculated using local food tables (6) and then categorized into quartiles after calculating the percentiles 25, 50, and 75 of the sample of controls. They were energy-adjusted according to the residuals method of Willett and Stampfer (7). Relative risks of prostate cancer, approximated by the ORs, were calculated by unconditional logistic regression (8). All ORs were controlled for potential confounders, including the matching variables (age, residence, and urban/rural status). All calculations were performed using the STATA software (release 6, STATA, College Station, Texas).

## Results

The distribution of cases and controls by age, residence, and urban/rural status was very similar. Cases were less educated and with a lesser income than controls (Table 1). On the other hand, family history of prostate cancer in a first degree relative was infrequent, but significantly higher in cases compared with controls. Finally, body mass index was rather similar in both series of patients.

Unadjusted means for total energy were similar for both series of patients. Cases showed higher means for total fat, saturated fat, monounsaturated fat,  $\alpha$ -linolenic acid, and cholesterol than controls. The remaining macro- and micronutrients displayed similar values in both series of patients. The correlation coefficients for fats were adjusted for calories.  $\alpha$ -linolenic acid was highly correlated with total fat, saturated fat, and monounsaturated fat, but not with linoleic acid and cholesterol. The correlation coefficient between linoleic and linolenic acid was particularly low ( $\rho = 0.12$ ).

ORs for occupational exposures, tobacco smoking, and alcohol drinking were close to null. On the other hand, "mate" drinking was associated with an increased risk (OR, 2.2) and a well-defined dose-response pattern (results not shown).

ORs of prostate cancer for intake of different types of fat are shown in Table 2. Total fat intake was associated with a weak positive association (fourth quartile of intake, 1.33; 95% CI, 0.75–2.34) after controlling for total energy intake, body mass index, and family history of prostate cancer. Similar ORs were observed for saturated fat and monounsaturated fat, whereas a small decrease in risk was found for the highest quartile of intake of linoleic acid (OR, 0.71; 95% CI, 0.42–1.20). The only fatty acid associated with a significant in-

Table 1 Distribution of cases and controls for selected variables<sup>a</sup>

| Variable                               | Cases      | Controls   | Significance |
|----------------------------------------|------------|------------|--------------|
| Age (yr)                               |            |            |              |
| 40–49                                  | 2 (0.9)    | 4 (0.9)    |              |
| 50–59                                  | 10 (4.6)   | 20 (4.6)   |              |
| 60–69                                  | 70 (32.3)  | 141 (32.7) |              |
| 70–79                                  | 107 (49.3) | 215 (49.9) |              |
| 80–89                                  | 28 (12.9)  | 51 (11.8)  | 0.99         |
| Residence                              |            |            |              |
| Montevideo                             | 102 (47.0) | 210 (48.7) |              |
| Other counties                         | 115 (53.0) | 221 (51.3) | 0.74         |
| Urban/rural status                     |            |            |              |
| Urban                                  | 152 (70.0) | 304 (70.5) |              |
| Rural                                  | 65 (30.0)  | 127 (29.5) | 0.97         |
| Education (yr)                         |            |            |              |
| 0–2                                    | 77 (35.5)  | 143 (33.2) |              |
| 3–4                                    | 75 (34.6)  | 127 (29.5) |              |
| 5+                                     | 65 (30.0)  | 161 (37.4) | 0.15         |
| Monthly income (United States dollars) |            |            |              |
| ≤158                                   | 65 (30.0)  | 152 (35.3) |              |
| 159+                                   | 61 (28.1)  | 148 (34.3) |              |
| Unknown                                | 91 (41.9)  | 131 (30.4) | 0.01         |
| Family history of prostate cancer      |            |            |              |
| No                                     | 210 (96.8) | 430 (99.8) |              |
| Yes                                    | 7 (3.2)    | 1 (0.2)    | 0.004        |
| Body mass index                        |            |            |              |
| ≤23.5                                  | 44 (20.3)  | 118 (27.4) |              |
| 23.6–25.2                              | 60 (27.6)  | 105 (24.4) |              |
| 25.3–27.3                              | 56 (25.8)  | 107 (24.8) |              |
| 27.4+                                  | 57 (26.3)  | 101 (23.4) | 0.24         |
| Alcohol drinking                       |            |            |              |
| Nondrinkers                            | 82 (37.8)  | 136 (31.6) |              |
| 1–60                                   | 39 (18.0)  | 103 (23.9) |              |
| 61–120                                 | 41 (18.9)  | 86 (20.0)  |              |
| 121+                                   | 55 (25.3)  | 106 (24.6) | 0.24         |
| No. of children                        |            |            |              |
| 0                                      | 40 (18.4)  | 75 (17.4)  |              |
| 1–2                                    | 65 (29.9)  | 119 (27.6) |              |
| 3–4                                    | 57 (26.2)  | 185 (42.9) |              |
| 5+                                     | 39 (17.9)  | 44 (10.2)  |              |
| Unknown                                | 16 (7.4)   | 8 (1.9)    | 0.24         |
| Mean energy intake                     | 2114.2     | 2033.1     |              |
| No. of patients                        | 217 (100)  | 431 (100)  |              |

<sup>a</sup> Values in parentheses are percentages.

creased risk was  $\alpha$ -linolenic acid (fourth quartile of intake, 1.91; 95% CI, 1.12–3.25). When  $\alpha$ -linolenic was further adjusted for saturated fat, monounsaturated fat, and linoleic acid, a strong association was observed (fourth quartile of intake, 3.91; 95% CI, 1.50–10.1). Also, the dose-effect was highly significant ( $P = 0.001$ ).

$\alpha$ -Linolenic acid effect was analyzed according to its main sources (animal and vegetable  $\alpha$ -linolenic acid) in a model, which included total calories, saturated fat, monounsaturated fat, animal linoleic acid, vegetable linoleic acid, and the two types of  $\alpha$ -linolenic acid (Table 2). Both sources of linolenic acid were strongly associated with prostate cancer risk (OR for animal  $\alpha$ -linolenic acid, 2.9 and OR for vegetable  $\alpha$ -linolenic acid, 2.0). Furthermore, both variables displayed a significant dose-response pattern. Because some categories of diseases in the control series (*i.e.*, anemia) could bias the results, we performed separate analyses, with and without each category of diseases. The results remained unchanged (results not shown).

Results from different models are shown in Table 3, following the original presentation of Gann *et al.* (9). When linoleic acid was further adjusted for  $\alpha$ -linolenic acid, the

<sup>3</sup> The abbreviations used are: FFQ, food-frequency questionnaire; OR, odds ratio; CI, confidence interval.

Table 2 ORs of prostate cancer for different types of fat

| g/day                                 | Cases/Controls | OR1 <sup>a</sup> | 95% CI    | OR2 <sup>b</sup> | 95% CI    |
|---------------------------------------|----------------|------------------|-----------|------------------|-----------|
| Total fat                             |                |                  |           |                  |           |
| ≤66.8                                 | 29/108         | 1.0              |           | NA <sup>c</sup>  |           |
| 66.9–88.7                             | 68/108         | 2.17             | 1.29–3.67 |                  |           |
| 88.8–114.5                            | 77/108         | 2.44             | 1.46–4.09 |                  |           |
| 114.6+                                | 43/107         | 1.33             | 0.75–2.34 |                  |           |
| <i>P</i> for linear trend             |                |                  | 0.32      |                  |           |
| Saturated fat                         |                |                  |           |                  |           |
| ≤28.5                                 | 29/108         | 1.0              |           | 1.0              |           |
| 28.6–37.7                             | 76/108         | 2.53             | 1.50–4.24 | 1.75             | 0.79–3.87 |
| 37.8–49.2                             | 66/108         | 2.13             | 1.26–3.59 | 0.64             | 0.22–1.81 |
| 49.3+                                 | 46/107         | 1.44             | 0.82–2.52 | 0.24             | 0.06–0.90 |
| <i>P</i> for linear trend             |                |                  | 0.45      |                  | 0.006     |
| Monounsaturated fat                   |                |                  |           |                  |           |
| ≤26.4                                 | 32/108         | 1.0              |           | 1.0              |           |
| 26.5–36.8                             | 59/108         | 1.66             | 0.99–2.79 | 0.98             | 0.46–2.07 |
| 36.9–46.4                             | 78/108         | 2.19             | 1.32–3.64 | 1.76             | 0.68–4.52 |
| 46.5+                                 | 48/107         | 1.38             | 0.80–2.38 | 1.91             | 0.60–6.02 |
| <i>P</i> for linear trend             |                |                  | 0.15      |                  | 0.15      |
| Linoleic acid                         |                |                  |           |                  |           |
| ≤5.7                                  | 51/108         | 1.0              |           | 1.0              |           |
| 5.8–7.7                               | 77/108         | 1.49             | 0.94–2.36 | 1.52             | 0.94–2.45 |
| 7.8–10.9                              | 51/108         | 0.94             | 0.58–1.55 | 0.95             | 0.57–1.59 |
| 11.0+                                 | 38/107         | 0.71             | 0.42–1.20 | 0.69             | 0.39–1.19 |
| <i>P</i> for linear trend             |                |                  | 0.07      |                  | 0.05      |
| $\alpha$ -Linolenic acid              |                |                  |           |                  |           |
| ≤0.8                                  | 34/108         | 1.0              |           | 1.0              |           |
| 0.9–1.1                               | 53/108         | 1.61             | 0.95–2.71 | 1.26             | 0.64–2.46 |
| 1.2–1.4                               | 69/108         | 2.19             | 1.31–3.64 | 2.23             | 1.01–4.94 |
| 1.5+                                  | 61/107         | 1.91             | 1.12–3.25 | 3.91             | 1.50–10.1 |
| <i>P</i> for linear trend             |                |                  | 0.009     |                  | 0.001     |
| Animal Linolenic acid <sup>d</sup>    |                |                  |           |                  |           |
| ≤0.61                                 | 36/108         | 1.0              |           | 1.0              |           |
| 0.62–0.84                             | 52/108         | 1.49             | 0.88–2.50 | 0.87             | 0.40–1.89 |
| 0.85–1.16                             | 71/108         | 1.95             | 1.18–3.21 | 1.60             | 0.65–3.93 |
| 1.17+                                 | 58/107         | 1.65             | 0.99–2.78 | 2.98             | 1.02–8.68 |
| <i>P</i> for linear trend             |                |                  | 0.03      |                  | 0.007     |
| Vegetable linolenic acid <sup>d</sup> |                |                  |           |                  |           |
| ≤0.07                                 | 51/107         | 1.0              |           | 1.0              |           |
| 0.08–0.10                             | 52/109         | 1.22             | 0.73–2.03 | 1.25             | 0.71–2.18 |
| 0.11–0.15                             | 56/108         | 1.57             | 0.91–2.72 | 1.74             | 0.94–3.25 |
| 0.16+                                 | 58/107         | 1.59             | 0.91–2.79 | 2.03             | 1.01–4.07 |
| <i>P</i> for linear trend             |                |                  | 0.07      |                  | 0.02      |

<sup>a</sup> OR1, adjusted for age, residence, urban/rural status, education, body mass index, family history of prostate cancer in a first degree relative, and total energy intake.

<sup>b</sup> OR2, further adjusted for saturated fat, monounsaturated fat, linoleic acid, linolenic acid, and vegetable and fruit intake.

<sup>c</sup> NA, not applicable.

<sup>d</sup> Further adjusted for each other.

results were similar to the initial model, which included terms for age, residence, urban/rural status, family history of prostate cancer in first degree relatives, body mass index, and total calorie intake. On the other hand, the introduction of terms for linoleic acid, meat intake, and saturated fat resulted in an increase in risk of prostate cancer associated with  $\alpha$ -linolenic acid (OR for the highest quartile of intake for  $\alpha$ -linolenic acid after further adjustment for linoleic acid and meat intake, 4.4; 95% CI, 1.6–11.6).

## Discussion

According to the results of the present study,  $\alpha$ -linolenic acid was associated with a significant increase in risk of prostate cancer after controlling for total energy intake and for other types of fat. The association was strong and showed a significant dose-response pattern. Furthermore, both  $\alpha$ -linolenic from animal and vegetable sources displayed increased risks of pros-

tate cancer. Four of five previous epidemiological studies on  $\alpha$ -linolenic acid and prostate cancer risk showed positive associations (2, 9–12). Three of them yielded significant associations (2, 9, 12), and only the study of Andersson *et al.* (10) showed no association. Thus, including our results, five of six studies on  $\alpha$ -linolenic acid and prostate cancer showed positive associations, suggesting the possibility that  $\alpha$ -linolenic acid intake could enhance the risk of developing prostate carcinoma. Alternatively,  $\alpha$ -linolenic acid could be a marker of a more complex dietary pattern. At difference with the Giovannucci *et al.* (2) study, our results suggest that  $\alpha$ -linolenic acid from vegetable sources could be also a risk factor for prostate cancer.

Several mechanisms have been suggested to explain the possible effect of  $\alpha$ -linolenic acid in prostatic carcinogenesis. Among these, interference with 5 $\alpha$ -reductase and formation of free radicals from fatty acid oxidation have been suggested as possible pathways for  $\alpha$ -linolenic carcinogenic effect (2, 9). In

Table 3 ORs of prostate cancer according to different models

| Model               | Covariates                    | I   | II            | III           | IV             |
|---------------------|-------------------------------|-----|---------------|---------------|----------------|
| Linoleic            |                               |     |               |               |                |
| 1 <sup>a</sup>      |                               | 1.0 |               |               |                |
| 2                   | Model 1 + linolenic acid      |     | 1.4 (0.9–2.3) | 0.9 (0.5–1.5) | 0.7 (0.4–1.2)  |
| 3                   | Model 2 + saturated fat       |     | 1.4 (0.9–2.3) | 0.9 (0.5–1.5) | 0.6 (0.4–1.1)  |
| 4                   | Model 3 + monounsaturated fat |     | 1.5 (0.9–2.4) | 0.9 (0.5–1.6) | 0.7 (0.4–1.2)  |
| 5                   | Model 4 + red meat            |     | 1.5 (0.9–2.4) | 0.9 (0.5–1.5) | 0.6 (0.3–1.1)  |
| $\alpha$ -linolenic |                               |     |               |               |                |
| 6                   | Same as model 1               | 1.0 | 1.6 (0.9–2.7) | 2.1 (1.3–3.6) | 1.9 (1.1–3.2)  |
| 7                   | Model 6 + linoleic acid       |     | 1.6 (0.9–2.8) | 2.1 (1.2–3.5) | 2.0 (1.1–3.4)  |
| 8                   | Model 7 + saturated fat       |     | 1.3 (0.6–2.5) | 2.5 (1.1–5.4) | 4.4 (1.7–11.3) |
| 9                   | Model 8 + monounsaturated fat |     | 1.2 (0.6–2.4) | 2.2 (1.0–4.9) | 3.9 (1.5–10.1) |
| 10                  | Model 9 + red meat            |     | 1.3 (0.6–2.5) | 2.3 (1.0–5.2) | 4.4 (1.6–11.6) |

<sup>a</sup> Adjusted for age, residence, urban/rural status, education, family history of prostate cancer in a first degree relative, body mass index, and total energy intake.

fact, previous studies on fat intake and prostate cancer have supported either an effect of total fat or saturated fat intakes (13). Most of these analytical studies suffered from lack of control of total energy intake, which is a rather severe limitation. In our study, saturated fat intake displayed an inverse association with prostate cancer risk after controlling for age, residence, urban/rural status, family history of prostate cancer, body mass index, total calorie intake, a term for all vegetables and fruits, and other types of fat (OR for the highest quartile of intake of saturated fat, 0.3; 95% CI, 0.1–0.9). This inverse association appears to be mainly related to the confounding effect by  $\alpha$ -linolenic acid intake (results not shown). On the other hand, the effect of fats was controlled for total calorie intake.

Like other hospital-based case-control studies, the present study has several drawbacks. The possibility of selection and classification bias is always to be considered. On the other hand, the inclusion of hospitalized controls could help to minimize recall bias because these patients could be submitted to similar forces of recall as cases. This statement is, of course, submitted to important limitations, and there are differences between patients having an advanced malignancy and controls diagnosed with benign conditions. Also, there exist the possibility that the models used in the multivariate analysis were unstable due to the high collinearity existing between different types of fat. Nevertheless, SE for each fat variable are not unusually large. Also, the incident nature of the cases does not preclude the possibility of recent changes in the diet. The study has also strengths. Perhaps the most important is the high response rate for both series of patients. Interviewers were blinded regarding the case or control diagnosis. This is a result of the fact that the present study was part of a multisite case-control study on cancers in the Uruguayan population. Finally, the exclusion of proxy interviews could help to avoid errors in reporting exposures like diet.

In summary, the present case-control study suggests a

rather strong effect of dietary  $\alpha$ -linolenic acid in prostate carcinogenesis. Furthermore, this effect appears to exist for this essential fatty acid independently of its source of origin.

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