

## Fatty Acids and Risk of Prostate Cancer in a Nested Case-Control Study in Male Smokers

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### Abstract

There is some evidence that  $\alpha$ -linolenic acid might be positively related to prostate cancer risk. Associations between serum fatty acid composition as well as fatty acid intakes and prostate cancer risk were examined in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. The cohort included 29,133 male smokers aged 50–69 years. During 5–8 years of follow-up, 246 prostate cancer cases were diagnosed. One control was selected and matched by age ( $\pm 1$  month) for each case from the cohort subjects alive and free of prostate cancer at the time the case was diagnosed. This study included 198 case-control pairs with baseline serum sample available for both. Fatty acids of serum cholesterol esters were measured as a percentage of total fatty acids, using capillary gas chromatography. Intakes of fatty acids were assessed from a validated self-administered dietary questionnaire. Serum and dietary fatty acids had no consistent association with prostate cancer risk. Serum  $\alpha$ -linolenic acid was not related to prostate cancer risk. Twofold risk was found in the highest quartile of serum myristic acid compared with the lowest quartile (odds ratio, 1.93; 95% confidence interval, 1.02–3.64).  $\alpha$ -Tocopherol supplementation modified the association between serum linoleic acid and prostate cancer risk ( $P$  for interaction 0.03); odds ratio was 0.17 (95% confidence interval, 0.04–0.68) in the highest quartile of serum linoleic acid compared with the lowest quartile in men who received  $\alpha$ -tocopherol, whereas no association was found in men who did not receive  $\alpha$ -tocopherol. In conclusion, we found no overall association between

serum or dietary  $\alpha$ -linolenic acid or any other unsaturated fatty acid and prostate cancer risk, but high serum linoleic acid was associated with lower risk in men supplemented with  $\alpha$ -tocopherol. High serum myristic acid associated with an increased risk of prostate cancer.

### Introduction

Migrant studies and ecologic evidence that incidence rates of clinical prostate cancer vary geographically much more than that of latent prostate cancer suggest that environmental factors play an important role at least in late prostatic carcinogenesis (1). Some dietary factors especially have been observed to increase prostate cancer risk (2).

The evidence on an association between fat intake and prostate cancer risk is mainly based on epidemiological studies. Most case-control studies have associated high intakes of animal fat or saturated fatty acids with an increased risk of prostate cancer, but only a few of them have adjusted fat intake for energy (3). High total fat intake was associated with the risk of advanced prostate cancer in the Health Professionals Follow-Up Study (4). Of fatty acids, the prostate cancer risk was three times higher for men in the highest quintile of  $\alpha$ -linolenic intake compared with those in the lowest quintile. In the Physicians' Health Study, high plasma concentration of  $\alpha$ -linolenic acid was related to a higher prostate cancer risk (5). Comparable data from animal studies are limited because of the lack of suitable animal models and unclear relevance to the human disease (6).

We examined associations between different dietary fatty acids and serum fatty acid concentration, and prostate cancer risk in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (the ATBC study).

### Materials and Methods

**Study Design and Subjects.** The subjects of this study were participants of the ATBC study, a randomized placebo-controlled trial, of which the main aim was to examine whether daily supplementation with  $\alpha$ -tocopherol (AT),  $\beta$ -carotene (BC), or both would prevent lung cancer or other cancer in male smokers. The study design as well as participant characteristics and methods have been described in detail earlier (7, 8).

A questionnaire asking about smoking habits and willingness to participate in the ATBC study was mailed to the total male population aged 50–69 and living in southwestern Finland ( $n = 290,406$ ) between 1985 and 1988 (8). In all, 79% of the men replied and 54,000 smoked at least five cigarettes per day, and 42,000 of smokers were willing to participate in the trial. Participants were excluded if they had a previous history of cancer or a disease limiting long term participation, or if they used vitamin E, vitamin A, or BC supplements in excess of predefined doses. In addition, some of the men who were initially interested in participation refused their participation

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before randomization. Thus, 29,133 men were randomly assigned to receive AT (50 mg/day), BC (20 mg/day), both agents, or placebo. Follow-up continued for 5–8 years (median, 6.1 years), until April 30, 1993. The ATBC study was approved by the Institutional Review Boards of both the National Public Health Institute in Finland and the United States National Cancer Institute.

At the first visit, each man completed questionnaires on general background characteristics and medical, smoking, and occupational histories. Height and weight were measured, and serum samples were collected and stored at  $-70^{\circ}\text{C}$  for future analyses.

A total of 246 prostate cancer cases were diagnosed during the trial period. They were ascertained using the Finnish Cancer Registry and the Register of Causes of Death. All of the cases were reviewed independently by two oncologists to confirm the diagnosis and stage, and two pathologists checked the original histological and cytological specimens. One control was selected for each prostate cancer case from the participants of the ATBC study. The controls were required to be alive and free of prostate cancer at the date when the case was diagnosed. They were also individually matched with the case by age ( $\pm 1$  month) and by trial supplementation group. Complete data sets were available for both in 198 matched case-control pairs (28 cases and 30 controls had missing data either on dietary factors, serum samples, or adjusting factors).

Prostate tumors were classified by following the criteria of the American Joint Committee on Cancer (9) to stage 0 and stage I clinically inapparent (latent) tumors, and to stage II, III, and IV clinically apparent tumors. Of the 198 prostate cancer cases, 42 cases (21.2%) were classified as stage 0 or I tumors, and 155 (78.3%) were classified as stage II, III, or IV tumors. One subject could not be staged. The data were separately analyzed for men having stage 0 or stage I tumors, and for men having stage II, III, or IV tumors, but because the results were similar, only combined data for all of the cases are presented in this article.

**Dietary Assessment.** Food consumption over the previous 12 months was assessed at baseline using a validated self-administered dietary questionnaire (10). The consumption of 276 food items and mixed dishes was recorded by asking the number of times an item was usually consumed per day, per week, or per month, and by using a picture booklet including color photographs of foods to assess portion sizes. The type and brand name of fat consumed on bread, an important source of fat in the Finnish diet, was asked. There were also additional questions about the location where main meals were usually eaten and type of cooking fat typically used to define the type of fat for the recipes of mixed foods. The dietary questionnaire was given to the subject to be completed at home and returned 2 weeks later during the second baseline visit when a study nurse checked the questionnaire. Altogether, 93% of the dietary questionnaires were found acceptable.

The food data were converted into daily nutrient intakes by the software and the food composition database of the National Public Health Institute in Finland (11). The content of fatty acids is based on analyses of Finnish foods (12, 13). The fatty acid database includes 77 individual fatty acids or fatty acid isomers. Nutrient intakes were energy-adjusted according to the residual method (14).

The reproducibility and validity of the dietary questionnaire were tested in a pilot study using a 24-day diet record as a reference method (10). The intraclass correlation was 0.64 for total fat, 0.67 for saturated fatty acids, 0.63 for monounsaturated

fatty acids, and 0.73 for polyunsaturated fatty acids. The energy-adjusted correlation coefficients between the questionnaire and the diet records were 0.39, 0.62, 0.38, and 0.69, respectively.

**Laboratory Analysis.** We analyzed serum cholesterol esters, which reflect fatty acid intakes of a few days (15). Lipids were extracted from serum samples by a modification of Folch *et al.* (16), and cholesterol esters were separated from the fat extract by TLC. The cholesterol ester fatty acids were *trans*-esterified by acidic methanol (17). The fatty acid composition was determined by a HRGC 412 Micromat gas chromatography (HNU-Nordion Instruments, Finland) with a 25-m long NB-351 fused silica capillary column (diameter, 0.32 mm and phase layer, 0.20  $\mu\text{m}$ ; HNU-Nordion Instruments). Split injection was used, and helium was used as carrier gas. The temperature was programmed from  $170^{\circ}\text{C}$  to  $230^{\circ}\text{C}$ . The percentage composition of fatty acid methyl esters normalized to 100% was calculated from 14:0 to 22:6 with a Sunicom Workstation (Helsinki, Finland). Between-series variation of the larger gas chromatography peaks (the amount of the fatty acid over 3%) was 2.4–8% and that of smaller peaks (the amount of the fatty acid under 2%) 9–12% with exception for docosahexaenoic acid, C22:6n-3 (25%).

**Statistical Methods.** The case-control differences were tested using either paired *t* tests or paired  $\chi^2$  tests. The odds ratios (ORs) were calculated with conditional logistic regression. All of the models were adjusted for area of residence (urban/rural), education, body mass index, alcohol consumption, and number of years of smoking. In addition, dietary variables were adjusted for energy. Because the unadjusted results were similar to those of the multivariate models, the unadjusted results were presented. Quartiles for grouped analyses were calculated in full data with cases and controls combined. Tests for trends were calculated using Wald tests with linear contrasts. Because AT supplementation reduced the risk of prostate cancer by 32% (31) we studied whether the association between serum fatty acids and the risk of prostate cancer was modified by AT supplementation. For this, serum fatty acid effect was estimated as nested within the supplementation group. The interaction tests were based on likelihood ratios between the interaction and the no-interaction models. Supplementation groups were defined as AT (AT and AT+BC groups) and no AT (placebo and BC groups).

## Results

The selected characteristics of the prostate cancer cases and the controls are summarized in Table 1. Because of the individual matching, age distributions were similar between the groups, 61.5 years (SE  $\pm 0.4$ ). The distributions of other background variables, such as body mass index, alcohol consumption, number of cigarettes per day, years of smoking, and area of residence, were also similar. No differences were found for mean intakes of fatty acids between the cases and the controls.

Linoleic acid covered 46%, oleic acid 22%, and palmitic acid 13% of the total fatty acid proportion in serum cholesterol esters (Table 2). No differences were found for mean serum  $\alpha$ -linolenic acid, n-3 polyunsaturated fatty acids derived from fish (eicosapentaenoic acid and docosahexaenoic acid), or any other serum fatty acid proportion between the cases and controls. The correlation coefficient between dietary fatty acid and serum fatty acid was 0.58 for linoleic acid, 0.36 for myristic acid, 0.35 for docosahexaenoic acid, and  $<0.30$  for the other fatty acids.

The risk of prostate cancer was higher in the upper quartile

Table 1 Characteristics and intakes of dietary fatty acids of prostate cancer cases and controls, mean<sup>a</sup> ± SE or proportion

	Cases (n = 198)	Controls (n = 198)	Case-control difference <sup>b</sup>
Age (years)	61.5 ± 0.4	61.5 ± 0.4	0.0
Body mass index (kg/m <sup>2</sup> )	26.6 ± 0.3	26.3 ± 0.3	0.2
Alcohol consumption (g/day)	17.0 ± 2.0	14.7 ± 1.4	2.3
Cigarettes (number per day)	18.9 ± 0.6	19.9 ± 0.7	-0.9
Smoking (number of years)	39.7 ± 0.6	40.1 ± 0.6	-0.4
Urban (%)	69.6	68.1	
More education than high school (%)	13.6	11.6	
Myristic acid, C14:0 (g/day)	7.0 ± 0.3	7.0 ± 0.3	0.0
Palmitic acid, C16:0 (g/day)	23.4 ± 0.7	23.7 ± 0.7	-0.3
Palmitoleic acid, C16:1 n-7 (g/day)	1.46 ± 0.04	1.47 ± 0.04	-0.01
Stearic acid, C18:0 (g/day)	10.8 ± 0.3	11.0 ± 0.3	-0.2
Oleic acid, C18:1 n-9 (g/day)	9.0 ± 0.3	9.2 ± 0.3	-0.1
Linoleic acid, C18:2 n-6 (g/day)	9.2 ± 0.4	9.7 ± 0.5	-0.4
α-Linolenic acid, C18:3 n-3 (g/day)	1.65 ± 0.06	1.62 ± 0.05	0.03

<sup>a</sup> Unadjusted values.<sup>b</sup> Matched sets.

of serum myristic acid compared with the lower quartiles (Table 3). The OR between the highest and lowest quartile of serum myristic acid was 1.93 [95% confidence interval (CI), 1.02–3.64]. The serum fatty acid proportion differed across the quartiles of serum myristic acid (main sources: milk, butter, and meat); in the highest quartile the mean proportion of serum linoleic acid (main source: vegetable oil) was 41% compared with 52% in the lowest quartile. When the association between myristic acid and prostate cancer risk was adjusted for linoleic acid, the OR for the highest quartile was 2.06 (95% CI, 1.00–4.25). When the risk of linoleic acid was adjusted for myristic acid, the OR was 1.10 (95% CI, 0.56–2.17). No significant associations were found between serum α-linolenic acid or any other fatty acid and prostate cancer risk.

The associations for serum palmitic acid and linoleic acid were modified by trial AT supplementation. High proportion of serum palmitic acid increased and high proportion of linoleic acid decreased the risk of prostate cancer among those who received AT but not among those who did not receive AT (Table 4). The associations were not independent of each other, because when cut by median, three fourths of the cases and controls had either a high palmitic and low linoleic or a low

palmitic and high linoleic acid proportion in serum. No other interactions were found for the serum fatty acids.

The intakes of fatty acids were not associated with prostate cancer risk (Table 5).

## Discussion

We found no overall association between unsaturated fatty acid composition in serum and the risk of prostate cancer. However, among men who received AT supplementation, high serum linoleic acid proportion had an inverse association with the prostate cancer risk. Of the saturated fatty acids, high serum myristic acid was associated with a 2-fold risk of prostate cancer. Dietary fatty acids had no consistent associations with the risk of prostate cancer.

The ATBC study included only smokers, which should be noted when the results are extrapolated to different populations. However, most large cohort studies found no association between cigarette smoking and incidence of prostate cancer (18). It has been reported that plasma saturated fatty acid concentration is higher, and linoleic acid concentration lower in smokers, alcohol drinkers, and obese people than in the general popula-

Table 2 Mean serum fatty acid composition (%) of prostate cancer cases and controls

	Cases (n = 198)		Controls (n = 198)		Case-control <sup>b</sup>	
	Mean <sup>a</sup>	(SE)	Mean <sup>a</sup>	(SE)	Difference <sup>a</sup>	P <sup>a</sup>
Myristic acid, C14:0	1.23	(0.02)	1.18	(0.02)	0.05	0.10
Palmitic acid, C16:0	12.84	(0.08)	12.69	(0.07)	0.15	0.15
Palmitoleic acid, C16:1 n-7	4.96	(0.14)	4.80	(0.12)	0.16	0.38
Stearic acid, C18:0	1.30	(0.03)	1.32	(0.02)	-0.02	0.56
cis-Vaccenic acid, C18:1 n-7	1.25	(0.02)	1.253	(0.014)	-0.006	0.75
Oleic acid, C18:1 n-9	22.5	(0.3)	22.3	(0.2)	0.2	0.58
Linoleic acid, C18:2 n-6	46.4	(0.5)	47.1	(0.4)	-0.7	0.22
α-Linolenic acid, C18:3 n-3	0.70	(0.02)	0.70	(0.02)	0.00	0.95
γ-Linolenic acid, C18:3 n-6	0.73	(0.02)	0.70	(0.02)	0.03	0.23
Dihomo-γ-linolenic acid, C20:3 n-6	0.617	(0.009)	0.615	(0.010)	0.002	0.89
Arachidonic acid, C20:4 n-6	4.99	(0.08)	4.87	(0.06)	0.13	0.19
Eicosapentaenoic acid, C20:5 n-3	1.76	(0.07)	1.70	(0.06)	0.06	0.50
Docosahexaenoic acid, C22:6 n-3	0.80	(0.02)	0.81	(0.02)	0.00	0.87

<sup>a</sup> Unadjusted values. The results were similar after adjustment for area of residence (urban/rural), education, body mass index, alcohol consumption, and the number of years of smoking.<sup>b</sup> t test in matched sets.

Table 3 Odds ratios<sup>a</sup> and 95% confidence intervals (CIs) for prostate cancer in quartiles of serum fatty acid composition in male smokers

Serum lipids	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Trend, <i>P</i>
Myristic acid, C14:0 (median %)	0.86	1.12	1.28	1.56	
Odds ratio	1.00	0.82	1.14	1.93	
95% CI		0.45–1.49	0.63–2.07	1.02–3.64	0.02
Palmitic acid, C16:0 (median %)	11.63	12.35	12.94	13.99	
Odds ratio	1.00	0.96	1.47	1.27	
95% CI		0.54–1.72	0.82–2.63	0.68–2.36	0.27
Palmitoleic acid, C16:1 n-7 (median %)	3.09	3.98	5.11	6.88	
Odds ratio	1.00	0.92	1.18	1.06	
95% CI		0.51–1.65	0.68–2.05	0.57–1.95	0.67
Stearic acid, C18:0 (median %)	0.96	1.19	1.36	1.63	
Odds ratio	1.00	0.81	0.86	0.72	
95% CI		0.46–1.43	0.49–1.51	0.40–1.29	0.33
<i>cis</i> -Vaccenic acid, C18:1 n-7 (median %)	1.01	1.18	1.31	1.49	
Odds ratio	1.00	0.71	0.75	0.81	
95% CI		0.40–1.26	0.41–1.36	0.44–1.48	0.55
Oleic acid, C18:1 n-9 (median %)	18.54	21.54	23.48	25.73	
Odds ratio	1.00	1.17	0.70	1.21	
95% CI		0.66–2.07	0.39–1.28	0.66–2.20	0.96
Linoleic acid, C18:2 n-6 (median %)	39.77	44.82	48.43	53.28	
Odds ratio	1.00	0.82	0.73	0.77	
95% CI		0.45–1.50	0.42–1.25	0.43–1.39	0.35
$\alpha$ -Linolenic acid, C18:3 n-3 (median %)	0.47	0.60	0.71	0.91	
Odds ratio	1.00	0.92	1.16	0.97	
95% CI		0.53–1.62	0.68–1.98	0.54–1.75	0.89
$\gamma$ -Linolenic acid, C18:3 n-6 (median %)	0.44	0.62	0.79	1.00	
Odds ratio	1.00	1.09	1.68	1.30	
95% CI		0.61–1.93	0.92–3.05	0.74–2.27	0.18
Dihomo- $\gamma$ -linolenic acid, C20:3 n-6 (median %)	0.45	0.57	0.66	0.78	
Odds ratio	1.00	1.22	1.26	1.09	
95% CI		0.68–2.17	0.71–2.20	0.58–2.04	0.76
Arachidonic acid, C20:4 n-6 (median %)	3.96	4.55	5.09	5.89	
Odds ratio	1.00	1.05	0.94	1.39	
95% CI		0.60–1.84	0.54–1.64	0.79–2.44	0.34
Eicosapentaenoic acid, C20:5 n-3 (median %)	0.92	1.25	1.76	2.74	
Odds ratio	1.00	1.00	0.72	1.12	
95% CI		0.55–1.80	0.39–1.32	0.61–2.04	1.00
Docosahexaenoic acid, C22:6 n-3 (median %)	0.55	0.70	0.84	1.05	
Odds ratio	1.00	0.60	1.08	0.71	
95% CI		0.33–1.09	0.59–1.97	0.40–1.26	0.63

<sup>a</sup> Unadjusted values. The results were similar after adjustment for area of residence (urban/rural), education, body mass index, alcohol consumption, and the number of years of smoking.

Table 4 Odds ratios between serum palmitic acid and linoleic acid and prostate cancer risk by the supplementation groups

	AT <sup>a</sup>	No AT	<i>P</i> for interaction
	Odds ratio (95% CI) <sup>b</sup>	Odds ratio (95% CI) <sup>b</sup>	
Palmitic acid, C16:0			
Quartile 1	1.00	1.00	
Quartile 2	0.74 (0.24–2.30)	1.12 (0.55–2.29)	
Quartile 3	2.47 (0.81–7.54)	1.19 (0.57–2.47)	
Quartile 4	4.02 (1.04–15.6)	0.83 (0.39–1.76)	
<i>P</i> for trend	0.01	0.69	0.05
Linoleic acid, C18:2 n-6			
Quartile 1	1.00	1.00	
Quartile 2	0.27 (0.07–1.05)	1.27 (0.62–2.62)	
Quartile 3	0.38 (0.12–1.20)	0.87 (0.45–1.67)	
Quartile 4	0.17 (0.04–0.68)	1.30 (0.64–2.60)	
<i>P</i> for trend	0.02	0.72	0.03

<sup>a</sup> AT, men received supplementation with  $\alpha$ -tocopherol; No AT, men received no supplementation with  $\alpha$ -tocopherol; CI, confidence interval.

<sup>b</sup> Unadjusted values. The results were similar after adjustment for area of residence (urban/rural), education, body mass index, alcohol consumption, and the number of years of smoking.

tion (19). It is also possible that among many comparisons the few weakly positive findings, including subgroup analyses, may be due to chance.

The Physicians' Health Study showed a 2-fold to 3-fold increase in prostate cancer risk in all three of the upper quartiles of plasma  $\alpha$ -linolenic acid compared with the lowest quartile (5). A nested case-control study in Norway also showed an increasing risk for prostate cancer with increasing quartiles of  $\alpha$ -linolenic acid in serum phospholipids; the OR for the highest quartile was 2.0 (95% CI, 1.1–3.6; Ref. 20). On the contrary, a small case-control study in the United States found no association for  $\alpha$ -linolenic acid measured from erythrocyte membrane and adipose tissue (21). Most case-control studies and one cohort study found no associations between dietary unsaturated fatty acids and prostate cancer risk as reviewed by Kolonel *et al.* (3). However, a recent case-control study in Uruguay found an OR of 3.9 (95% CI, 1.5–10.1) for prostate cancer among men whose intake of  $\alpha$ -linolenic acid was >1.5 g a day compared with those <0.8 g a day (22). No association between dietary  $\alpha$ -linolenic acid and prostate cancer risk was found in a Swedish case-control study of 526 prostate cancer cases (23). In that study, mean intake of  $\alpha$ -linolenic acid was 1.1 g a day. The

Table 5 Odds ratios<sup>a</sup> and 95% confidence intervals (CIs) for prostate cancer in quartiles of energy-adjusted fatty acid intakes in male smokers

Fatty acid	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Trend, <i>P</i>
Myristic acid, C14:0 (median g/day)	3.9	6.0	7.5	9.4	
Odds ratio	1.00	1.31	1.09	1.15	
95% CI		0.74–2.30	0.62–1.90	0.66–2.02	0.79
Palmitic acid, C16:0 (median g/day)	17	21	24	29	
Odds ratio	1.00	0.95	1.28	0.82	
95% CI		0.53–1.71	0.73–2.26	0.46–1.44	0.73
Palmitoleic acid, C16:1 n-7 (median g/day)	1.1	1.3	1.5	1.8	
Odds ratio	1.00	0.96	0.93	0.89	
95% CI		0.56–1.65	0.54–1.60	0.51–1.55	0.66
Stearic acid, C18:0 (median g/day)	8.4	9.8	11.1	13.0	
Odds ratio	1.00	1.10	1.21	1.13	
95% CI		0.61–1.98	0.70–2.10	0.65–1.96	0.61
<i>cis</i> -Vaccenic acid, C18:1 n-7 (median g/day)	0.4	0.6	0.7	0.9	
Odds ratio	1.00	0.93	1.27	0.90	
95% CI		0.52–1.66	0.72–2.24	0.52–1.54	0.99
Oleic acid, C18:1 n-9 (median g/day)	5.6	7.6	9.3	12.7	
Odds ratio	1.00	0.80	0.79	0.95	
95% CI		0.44–1.46	0.46–1.36	0.54–1.69	0.85
Linoleic acid, C18:2 n-6 (median g/day)	4.5	5.9	8.5	16.9	
Odds ratio	1.00	0.77	1.13	0.92	
95% CI		0.45–1.32	0.65–1.98	0.54–1.59	0.88
$\alpha$ -Linolenic acid, C18:3 n-3 (median g/day)	1.0	1.3	1.8	2.3	
Odds ratio	1.00	1.51	1.08	1.16	
95% CI		0.87–2.65	0.61–1.92	0.64–2.13	0.90
$\gamma$ -Linolenic acid, C18:3 n-6 (median g/day)	0.05	0.09	0.13	0.18	
Odds ratio	1.00	0.72	0.84	0.92	
95% CI		0.41–1.26	0.47–1.51	0.53–1.60	0.93
Dihomo- $\gamma$ -linolenic acid, C20:3 n-6 (median g/day)	0.006	0.009	0.013	0.019	
Odds ratio	1.00	1.25	0.91	1.28	
95% CI		0.71–2.18	0.53–1.58	0.75–2.18	0.62
Arachidonic acid, C20:4 n-6 (median g/day)	0.04	0.06	0.07	0.10	
Odds ratio	1.00	0.89	1.10	1.31	
95% CI		0.52–1.54	0.64–1.90	0.77–2.21	0.23
Eicosapentaenoic acid, C20:5 n-3 (median g/day)	0.05	0.09	0.12	0.20	
Odds ratio	1.00	1.69	1.56	1.22	
95% CI		0.97–2.97	0.90–2.70	0.68–2.20	0.58
Docosahexaenoic acid, C22:6 n-3 (median g/day)	0.11	0.18	0.26	0.43	
Odds ratio	1.00	1.46	1.18	1.31	
95% CI		0.84–2.55	0.67–2.06	0.74–2.32	0.51

<sup>a</sup> Unadjusted values. The results were similar after adjustment for area of residence (urban/rural), education, body mass index, alcohol consumption, and the number of years of smoking.

Health Professionals Follow-Up Study, including 300 new prostate cancer cases, found that high intake of  $\alpha$ -linolenic acid increased the risk of advanced prostate cancer (risk ratio, 3.4; 95% CI, 1.7–7.0, intake >1.5 g *versus* <0.8 g a day; Ref. 4). In our study, intake of  $\alpha$ -linolenic acid was 25% higher than that in Sweden (23), in Uruguay (22), or in the United States (4). Positive associations were observed in countries where red meat is the main source of  $\alpha$ -linolenic acid (4, 22) instead of countries where also dairy products are an important part of diet, as in Finland (this study) and in Sweden (23). Thus, other components of meat and dairy products may explain the associations between  $\alpha$ -linolenic acid and prostate cancer risk. Processed meat includes various amounts of nitrosamines, heterocyclic amines, or polycyclic aromatic hydrocarbons (24), and high intake of animal protein may also increase prostate cancer risk by increasing serum levels of insulin-like growth factor I (25). Furthermore, the diet high in meat tends to be low in plant foods containing many components that may decrease the risk of cancer. On the other hand, dairy products include potential protective factors, such as vitamin D or conjugated linoleic acid, against cancer (26, 27).

There are two studies on serum saturated fatty acid pro-

portion and prostate cancer risk. In the Physicians' Health Study, plasma palmitic acid and stearic acid had no significant associations with prostate cancer risk (5). A nested case-control study based on stored samples from a serum bank in Norway found a positive association for palmitic acid (OR, 2.3; 95% CI, 1.1–4.7, the highest *versus* lowest quartile) and for myristic acid (OR, 1.8; 95% CI, 1.0–3.3; Ref. 20). We found a similar association for serum myristic acid. There was, however, no evidence of a dose-response relationship, because the high risk was related to the highest quartile, but the three lower quartiles had a risk value around unity. Ruminant fat, derived mainly from dairy products, is the major source for myristic acid in Finland (27), but dietary intake data did not show association for these products. A previous paper of this same data also showed no associations between consumption of milk products, red meat, fish, or poultry, and prostate cancer risk (28).

Five case-control studies have examined the relationship between energy-adjusted intake of saturated fat or animal fat and prostate cancer risk (3). Only one of them found a statistically significant positive association between these factors (29). That well-designed study included three ethnic groups in the United States and Canada, and it also excluded men with an

elevated level of prostate-specific antigen. Several other case-control studies have only reported the level of food consumption. Especially in countries where consumption of meat and dairy products are high, positive associations have been found between these foods and prostate cancer risk (3).

A cohort study of 51,529 men carried out in the United States found that total fat intake was positively related to the risk of advanced prostate cancer (risk ratio, 1.79; 95% CI, 1.04–3.07, the highest *versus* lowest quintile of intake; Ref. 4). An association was observed with animal fat but not with vegetable fat. High red meat consumption was most strongly associated with the advanced prostate cancer risk (risk ratio, 2.64; 95% CI, 1.21–5.77), whereas high fat intake from milk products or fish was not associated with the risk. That United States cohort defined categories for advanced and nonadvanced cases, which differs slightly from our classification of cases into latent and clinical. The results, however, did not change when we used the advanced/nonadvanced classification (data not shown). Another cohort study of 25,708 Norwegian men found no association between the intake of total fat or saturated fatty acids and prostate cancer risk. Although the follow-up period of this study was >10 years, the number of prostate cancer cases was relatively small ( $n = 72$ ; Ref. 30).

We found a suggestion that high proportion of serum palmitic acid seemed to be a risk factor and high proportion of serum linoleic acid a protective factor for prostate cancer risk in men supplemented with AT. These associations may have relevance to our finding that AT supplementation decreased the risk of prostate cancer by 32% (31). Diets high in polyunsaturated fatty acids have been shown to promote tumor growth in animal models (32, 33). Vitamin E may protect polyunsaturated fatty acids (*e.g.*, linoleic acid) in cell membranes from lipid peroxidation, an important promoter of carcinogenesis (34, 35). High intake of vitamin E has decreased the risk of cancer in many animal studies as reviewed by Wang *et al.* (36), Knekt (35), and Kimmick *et al.* (37). This decrease was also found in experimental studies using diets rich in polyunsaturated fatty acids to promote carcinogenesis (38). It could also be speculated that AT supplementation interacts with the fatty acid profile resulting in reduced cellular production of androgens, hormones promoting the development of prostate cancer.

Inaccuracies in estimating fatty acid intakes based on dietary questionnaires linked with incomplete nutrient databases cause limitations in nutritional epidemiology (39). Biochemical indicators allow a more objective assessment of dietary information given by participants. The correlation coefficients between intakes of fatty acids and biochemical indicators, however, have been rather modest, usually between 0.3 and 0.5 (14). Serum fatty acids that cannot be endogenously synthesized, such as omega-3 fatty acids, omega-6 fatty acids, and *trans*-fatty acids, are the best markers for dietary intake. Many factors have to be taken into account when using serum biomarkers. Individual fatty acids can be measured from erythrocytes, platelets, adipose tissue, and from several lipid sub-fractions in plasma, such as cholesterol esters, phospholipids, and triglycerides (14). The fatty acid composition varies between different fractions. For example, linoleic acid covers half of all fatty acids in the cholesterol ester fraction, and has two to three times higher proportion than that of oleic acid. The linoleic:oleic acid ratio is about two in plasma phospholipids, whereas oleic acid predominates in triglycerides (40, 41). Furthermore, there is more palmitic acid than stearic acid in these substrates, but the ratio between these two fatty acids varies from 2 in plasma phospholipids to >10 in plasma cholesterol esters (40, 41). Thus, comparison of results between studies is

difficult because fatty acids have often been measured from different fractions. Changes in saturated fatty acids and monounsaturated fatty acids may depend more on endogenous synthesis than on diet. A study including Italian and United States participants showed that although intake of saturated fatty acids was two times higher in the United States subgroup, the composition of saturated fatty acids in the cholesterol ester fraction of plasma was lower in the United States subgroup compared with the Italian one (42). Linoleic and other polyunsaturated fatty acids, which are high in the United States diet, may decrease the level of saturated fatty acid in plasma.

In summary, this study showed that serum and dietary fatty acids had no consistent association with prostate cancer risk among male smokers. However, there was a suggestion that high proportion of myristic acid in serum cholesterol esters, possibly indicating high intake of ruminant fats, or some factor correlated with them may increase the prostate cancer risk. On the other hand, high serum linoleic acid proportion may be protective against prostate cancer in men who are receiving AT supplementation.

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## Fatty Acids and Risk of Prostate Cancer in a Nested Case-Control Study in Male Smokers

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