

Short Communication

Serum *Trans*-Fatty Acids Are Associated with Risk of Prostate Cancer in β -Carotene and Retinol Efficacy Trial

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Abstract

Biomarkers of *trans*-fatty acid consumption have been associated with increased risks of breast and colon cancer, although no studies have examined their associations with prostate cancer risk. Using data from the β -Carotene and Retinol Efficacy Trial, this nested case-control study examined the relationships between serum phospholipid *trans*-fatty acids and prostate cancer incidence in 272 case and 426 control men. *Trans*-fatty acids were measured using organic extraction followed by separations with TLC and gas chromatography. Adjusted odds ratios for risk of prostate cancer with increasing levels of *trans*-fatty acids were calculated using logistic regression. There were consistent trends for increasing prostate cancer risk with

higher levels of C18 but not C16 *trans*-fatty acids, although only trends for $\Delta 11t$ 18:1 *trans*-vaccenic and $\Delta 9c,12t$ 18:2 fatty acids reached statistical significance. Odds ratios (95% confidence interval) contrasting low versus high quartiles for these fatty acids were 1.69 (1.03-2.77) and 1.79 (1.02-3.15), respectively. There were no consistent differences in associations between low-grade and high-grade cancer among the subset of 209 cases with information on tumor grade. Additional studies are needed to confirm these findings and better control for factors, such as use of prostate-specific antigen screening, which may confound this association. (Cancer Epidemiol Biomarkers Prev 2005;14(4):988-92)

Introduction

Prostate cancer is the most common malignancy in American men (1). However, beyond age, African-American race, and family history, risk factors for prostate cancer are not well understood. There is some evidence that dietary fat is associated with increased prostate cancer risk, and further that specific fatty acids may have unique effects on prostate cancer risk due to their distinct metabolic effects. In experimental models using cell cultures and animal xenografts, n-6 fatty acids generally promote and n-3 fatty acids generally prevent tumorigenesis (2). Little is known about the effects of *trans*-fatty acids in prostate, although they have been associated with increased risks of breast cancer (3, 4) and cardiovascular disease (5, 6), as well as increased levels of circulating cytokines (7). *Trans*-fatty acids are unsaturated fatty acids with at least one double bond in the *trans* configuration, formed during hydrogenation and vegetable oil processing, which are found primarily in fast foods, bakery products, packaged snacks, and margarines (8, 9). *Trans*-fatty acids resemble saturated fatty acids in their biophysical properties but are not as extensively metabolized, and thus serum *trans*-fatty acid levels reflect dietary intake (10-12). Here we examine the associations of specific *trans*-fatty acids, measured in serum phospholipids, with prostate cancer risk.

Materials and Methods

Study Participants. Data are from the β -Carotene and Retinol Efficacy Trial (CARET), a randomized trial of supplemental β -carotene and retinol for the prevention of lung cancer among 18,314 heavy smokers and asbestos-exposed workers. CARET began in 1985 and ended prematurely in 1996 when it was determined that the supplements increased risks of lung cancer, cardiovascular disease, and total mortality, but had no effects on prostate cancer incidence or mortality (13). Surveillance of the cohort continued following termination of the trial, and by 1998 there were 700 confirmed prostate cancer cases among CARET participants. Blood was collected at multiple times throughout the trial and was aliquotted and frozen for later analyses.

For this nested case-control study, participants were selected at two time points using slightly different matching criteria. Eligible cases were men with an available blood sample drawn at least 3 years before the first diagnosis of cancer at any site except nonmelanoma skin cancer. Eligible controls were men who were alive with no report of any cancer other than nonmelanoma skin cancer with an available blood sample drawn at least 3 years before the most recent follow-up, as of December 1995 for the first sample and September 1999 for the second sample. The first sample consisted of 115 cases and 115 controls, matched on exposure population (asbestos exposed or heavy smoker), period of enrollment (pilot or full-scale trial), center at enrollment, age group (5-year intervals), smoking status at baseline (never, former, or current), and year of enrollment (within the same 2-year time interval). The blood draw selected for the control was matched by calendar time (within 1 year) to the blood

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Table 1. Characteristics of prostate cancer cases and controls

	Cases (<i>n</i> = 272)	Controls (<i>n</i> = 426)
	<i>n</i> (%)	
Age at baseline (y)		
<55	39 (14)	64 (15)
55-59	69 (25)	113 (27)
60-64	74 (27)	111 (26)
≥65	90 (33)	138 (32)
Ethnicity*		
White	253 (93)	403 (95)
Non-white	19 (7)	23 (5)
Education†		
<12 y	41 (21)	56 (18)
High school graduate	57 (29)	104 (33)
Some college	55 (28)	95 (30)
4-y degree or higher	45 (23)	60 (19)
BMI at blood draw		
Normal, <25	57 (21)	94 (22)
Overweight, 25-29	125 (46)	220 (52)
Obese, ≥30	90 (33)	112 (26)
Alcohol consumption (drinks/d)		
None	84 (31)	152 (36)
<1	109 (40)	157 (37)
1-2	54 (20)	68 (16)
≥3	25 (9)	49 (11)
Smoking status at baseline‡		
Never/former	137 (50)	206 (48)
Current	135 (50)	220 (52)
Smoking pack-years§		
<40	93 (35)	145 (35)
40-60	115 (43)	167 (40)
>60	57 (22)	102 (25)
Exposure population		
Asbestos exposed	124 (45)	190 (45)
Heavy smoker exposed	148 (55)	236 (55)
Gleason score		
Unknown	63 (33)	NA
<7	128 (47)	NA
≥7	81 (30)	NA
	\bar{x} (SD)	
Time from blood draw to cancer diagnosis (mo)	56 (16)	NA
	Mean (SE) weight % of total fatty acids	
Monounsaturated, <i>trans</i> C16		
Δ9 [†] 16:1	0.19 (0.004)	0.20 (0.003)
Δ7 [†] 16:1	0.07 (0.002)	0.07 (0.001)
Monounsaturated, <i>trans</i> C18		
Δ8 [†] 18:1	0.19 (0.005)	0.19 (0.004)
Δ9 [†] 18:1 (elaidic)	0.28 (0.007)	0.28 (0.006)
Δ10 [†] 18:1	0.25 (0.007)	0.25 (0.005)
Δ11 [†] 18:1 (<i>trans</i> -vaccenic)	0.43 (0.011)	0.41 (0.008)
Δ12 [†] 18:1	0.52 (0.013)	0.51 (0.010)
Diunsaturated, <i>trans</i> C18:2		
Δ9 [†] ,12 [†] 18:2 [¶]	0.08 (0.002)	0.06 (0.002)
Δ9 [†] ,12 [†] 18:2 ^{**}	0.14 (0.004)	0.13 (0.003)
Δ9 [†] ,12 [†] 18:2	0.11 (0.002)	0.10 (0.002)

*Matching variable for second selection only.

†Missing data (case *n* = 74; control *n* = 111).

‡Matching variable for first selection only.

§Missing data (case *n* = 7; control *n* = 12).

||Geometric mean (geometric SE).

¶*T* test, *P* < 0.0001.***T* test, *P* < 0.05.

draw selected for the case. The second sample consisted of 161 cases and 318 controls (1:2 for most cases), matched for the variables listed above with the exception of excluding smoking status and including ethnicity. Data were also available on several potential confounding variables, including race/ethnicity, smoking history, body mass index (BMI), alcohol use, and education. BMI was calculated from weight and height measurements taken at the visit matching or closest to the blood draw. Four participants (three controls and one case) were deleted because of poor serum sample condition leading to unreliable laboratory results; six (four

controls and two cases) were excluded due to missing BMI; and one case observation was excluded because it was included as a control in the first sample. The final sample consisted of 272 case and 426 control men.

End Point Determination. When a cancer end point was reported, the medical records and pathology reports were obtained from the diagnosing hospital/physician. For prostate cancer, pathology reports from needle biopsy or radical prostatectomy were reviewed. End point materials were reviewed by three physician adjudicators, and a case

Table 2. Adjusted ORs for association of *trans*-fatty acids with prostate cancer risk

	2nd	3rd	4th	<i>P</i> , trend
Monounsaturated, <i>trans</i> C16				
Δ9 <i>t</i> 16:1	0.49 (0.31-0.79)* 0.17†	0.70 (0.45-1.10) 0.20	0.71 (0.44-1.15) 0.24	0.35
Δ7 <i>t</i> 16:1	0.72 (0.45-1.17) 0.05	1.06 (0.66-1.71) 0.07	0.98 (0.59-1.62) 0.09	0.70
Monounsaturated, <i>trans</i> C18				
Δ8 <i>t</i> 18:1	1.17 (0.75-1.84) 0.15	1.13 (0.71-1.79) 0.20	1.38 (0.86-2.22) 0.26	0.22
Δ9 <i>t</i> 18:1(elaidic)	1.05 (0.67-1.67) 0.21	1.37 (0.86-2.17) 0.28	1.39 (0.87-2.23) 0.38	0.10
Δ10 <i>t</i> 18:1	1.03 (0.65-1.63) 0.18	1.22 (0.77-1.94) 0.25	1.41 (0.87-2.28) 0.35	0.12
Δ11 <i>t</i> 18:1 (<i>trans</i> -vaccenic)	1.14 (0.71-1.84) 0.31	1.20 (0.73-1.97) 0.43	1.69 (1.03-2.77) 0.55	0.04
Δ12 <i>t</i> 18:1	1.15 (0.72-1.84) 0.39	1.37 (0.86-2.20) 0.53	1.53 (0.94-2.50) 0.69	0.07
Diunsaturated, <i>trans</i> C18:2				
Δ9 <i>c</i> ,12 <i>t</i> 18:2	1.69 (1.01-2.85) 0.04	1.91 (1.14-3.18) 0.06	1.79 (1.02-3.15) 0.10	0.04
Δ9 <i>t</i> ,12 <i>c</i> 18:2	1.18 (0.74-1.89) 0.10	1.12 (0.69-1.81) 0.13	1.31 (0.80-2.12) 0.17	0.35
Δ9 <i>t</i> ,12 <i>t</i> 18:2	0.98 (0.63-1.54) 0.08	0.85 (0.54-1.34) 0.10	1.19 (0.76-1.87) 0.13	0.58

NOTE: Adjusted for exposure population, period of enrollment, enrollment center, enrollment age group, year of randomization, ethnicity, baseline smoking status, age at blood draw, BMI, alcohol use, and an indicator for sample selection.

*OR (95% confidence interval).

†Lower bound quartile cutpoint (weight % of total fatty acids).

determination required consensus on the site of primary tumor, histology, and date of diagnosis. A single physician (G.E.G.) abstracted $n = 209$ Gleason score based on review of surgical, pathologic, and clinical records.

Measurements of *Trans*-Fatty Acids. A 250-μL aliquot of serum sample from each case and control was used for analyses, which were done blinded to case/control status. Specimens were run in batches with two quality control serum pool samples and three commercial standards in each extraction batch. Total lipids were extracted from the serum by the Folch method (14) and the phospholipid fraction was separated by TLC. The fatty acids in the phospholipid fraction were directly transesterified to produce fatty acid methyl esters, which were injected onto a gas chromatograph. *Trans*-fatty acid levels were expressed as weight percentages of total fatty acids. To measure the long-term system stability of serum samples, we monitored NIH D, NIH F, and GC-87 commercial standards (NuCheck-Prep, Inc., Elysian, MN) with 5% precision and 7% bias over 5 consecutive years of analysis. The coefficients of variation in the quality control pool samples for the *trans*-fatty acids of interest were: Δ7*t* 16:1, 20% and 21%; Δ9*t* 16:1, 22% and 22%; Δ6-8*t* 18:1, 4% and 10%; Δ9*t* 18:1(n-9*t*), 3% and Δ 21%; Δ10*t* 18:1, 3% and 14%; Δ11*t* 18:1, 4% and 9%; Δ12*t* 18:1, 2% and 7%; and Δ9*t*,12*t* 18:2, 13% and 28%; Δ9*c*,12*t* 18:2, 26% and 22%; Δ9*t*,12*c* 18:2, 10% and 12%, for the first and second samples, respectively. The large coefficients of variation in *trans*-fatty acids reflect their very low level in our quality control pool.

Statistical Methods. Logistic regression was used to estimate the relative odds of prostate cancer risk with increasing levels of fatty acids. Fatty acids were categorized into quartiles, based on their distributions in controls. To test for linear trend across categories, an ordinal score variable, ranging from 1 to 4, was generated based on quartile of exposure, and this variable was tested using the likelihood ratio test.

All models were controlled for matching variables, BMI (normal <25.0, overweight 25.0-29.9, and obese ≥30), alcohol use (none, <1 drink/d, 1-2 drinks/d, and ≥3 drinks/d),

ethnicity (white or non-white), baseline smoking status, age at blood draw, and an indicator for sample selection. We tested for differences in results between the two study samples using an interactive term in logistic regression models. There were only modest differences in results between models with and without control for covariates, and only adjusted models are given. Control for education, pack-years of smoking, and CARET treatment arm did not affect the odds ratios (OR), and these variables are not included in final models. Gleason scores were available on 209 cases and were categorized as low grade (<7) and high grade (7-10) for stratified analyses. Polychotomous logistic regression was used to model risks of high- and low-grade Gleason scores, using the same covariates listed above. All of the statistical tests were two sided, and statistical significance was inferred when $P < 0.05$. Statistical analyses were carried out using SAS 8.2 (SAS Institute, Inc., Cary, NC).

Results

The distributions of study sample demographic and health-related characteristics are given in Table 1. Approximately 60% of the sample were of age 60 years or older, 6% were non-white, half were smokers at randomization, and almost 80% were overweight or obese. There were no differences in participant characteristics between cases and controls. The mean time from blood draw to diagnosis of prostate cancer was 56 months (SD = 16). Half of the serum samples analyzed were from baseline blood draws, and the mean time from baseline to blood draw among remaining samples was 45 months. Table 1 also gives geometric mean *trans*-fatty acid levels in cases and controls. Levels of several fatty acids were higher among cases than controls, however, only differences for the diunsaturated Δ9*c*,12*t* 18:2 and Δ9*t*,12*c* 18:2 reached statistical significance.

Table 2 gives ORs for associations of *trans*-fatty acids with prostate cancer risk. There were no associations of the C16 monounsaturated *trans*-fatty acids with prostate cancer risk. There were, however, trends of increased prostate cancer

risk associated with all monounsaturated and diunsaturated C18 *trans*-fatty acids. These trends reached statistical significance for $\Delta 11t$ 18:1 *trans*-vaccenic fatty acid and $\Delta 9c, 12t$ 18:2, and there were statistically significant ORs of 1.69 and 1.79, respectively, contrasting their highest versus lowest quartiles.

Associations were somewhat stronger for low-grade compared with high-grade cancer, although differences were not statistically significant. ORs (95% confidence intervals) for low- and high-grade cancers, comparing the low and high quartiles of phospholipid concentrations, were 2.10 (1.06-4.14) and 1.94 (0.90-4.16) for $\Delta 11t$ 18:1 *trans*-vaccenic fatty acid and 2.80 (1.22-6.41) and 1.50 (0.63-3.56) for $\Delta 9c, 12t$ 18:2. There were no substantial or statistically significant differences in associations of fatty acids with prostate cancer risk between the two study samples (data not shown).

Discussion

This study found that serum phospholipid C18 *trans*-fatty acids, but not C16 *trans*-fatty acids, were associated with an increased risk of prostate cancer. These trends were consistent across all C18 *trans*-fatty acids, although only some reached statistical significance. There was no consistent evidence for differences in associations between low-grade and high-grade disease.

There are few published studies of *trans*-fatty acids and prostate cancer risk. Bakker et al. (15) reported a nonsignificant 0.5 (95% confidence interval, -0.15 to 0.85) correlation between total adipose C18:1 *trans*-fatty acids and prostate cancer incidence across 11 countries in Europe. Neither Hodge et al. (16) nor Schuurman et al. (17) found associations of dietary *trans*-fatty acids, as measured by food frequency questionnaire, with prostate cancer risk. Although there are several published studies reporting associations of *trans*-fatty acids with risks of breast and colon cancers (2, 3, 18, 19), research on *trans*-fatty acids and prostate cancer risk is too limited to draw conclusions.

There is a growing body of evidence supporting the role of chronic inflammation with prostate carcinogenesis (20, 21), and thus the associations of *trans*-fatty acids with increased inflammatory response may explain their associations with prostate cancer risk. *Trans*-fatty acids interfere with the Δ -6 desaturase enzyme in metabolism of essential fatty acids, which inhibits the anti-inflammatory activity of n-3 fatty acids (22). This effect of *trans*-fatty acids is seen in human observational and experimental studies. Recent cross-sectional studies reported positive associations between dietary (23) and plasma fatty acids and serologic measures of systemic inflammation, and a controlled feeding study found that *trans*-fatty acids increased C-reactive protein concentrations (24). Additional studies are needed to examine whether *trans*-fatty acids affect inflammation in prostate tissue.

Dietary intake of *trans*-fatty acids is through processed oils and products made with these oils. The amount of *trans* fats in oils depends on their source and processing, which can vary substantially both across products and across countries due to food regulations (25, 26). Most monounsaturated C18 *trans* fats come from the hydrogenation of oils. Diunsaturated *trans*-fatty acids are formed during the deodorization process of vegetable oils, which affects most oils produced in the United States, in particular canola and soybean oils. Monounsaturated *trans*-vaccenic fatty acid comes from both bacterial and industrial hydrogenation and is found in milk fat, ruminant flesh, and hydrogenated oils. There are several limitations to this study. All CARET participants were at very high lung cancer risk due to heavy smoking or occupational asbestos exposure. Results in this high-risk cohort may not be generalizable. We had information on the grade of prostate

cancer for only a subset of participants. Recent studies find that risk factors for prostate cancer differ between local and regional/distant disease (27, 28), which suggests that some factors affect cancer progression but not initiation. We also had no information on use of prostate-specific antigen screening, which strongly affects risk of being diagnosed with prostate cancer and can significantly distort findings from observational epidemiologic studies (29). Levels of *trans*-fatty acids in phospholipids are very low, and thus measurement error due to random variability could lead to misclassification. However, this would lead to a reduction in the observed OR. Lastly, because intake of *trans*-fatty acids in the United States is a marker of consuming commercially fried and processed foods, other factors associated with eating these foods could be the causal agent.

In summary, this preliminary investigation from a large cohort found associations of *trans*-fatty acids with increased prostate cancer risk. Additional studies are needed to confirm these findings and better control for factors that may confound this association.

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