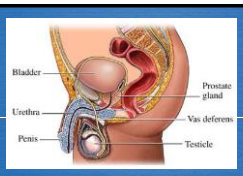
Omega-3 Fatty Acids, Inflammation, and Outcome in Men with and without Prostate Cancer

Julie A. Feifers, BA, BS
MS Candidate
Graduate Programs in Human Nutrition
Oregon Health & Science University

Overview

- Background & Significance
- Study Objective
- Study Design & Methods
- Results
- Discussion & Conclusions
- Questions

Prostate Cancer

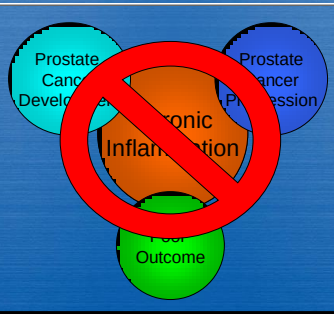


- Prostate gland
  - Walnut-sized gland located at the base of the bladder
- Prostate cancer
  - Most common non-cutaneous cancer in men
  - 2nd leading cause of cancer-related death
    - 28,000 deaths each year in the U.S.

Prostate Cancer Risk Factors

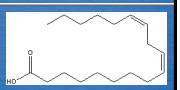
- Age
- Race
- Family history of prostate cancer
- Environmental or occupational exposure to toxins
- Diet
- Inflammation and oxidative stress

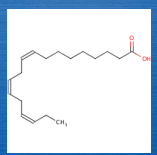
Inflammation & Prostate Cancer



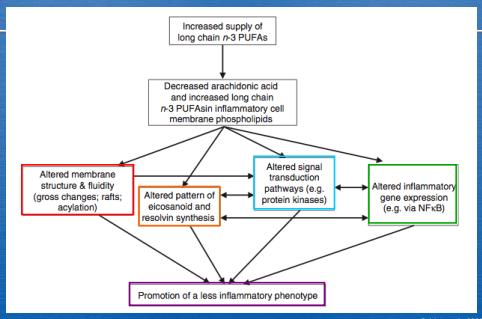
Omega-3 & Omega-6 Fatty Acids

- Essential fatty acids
  - Must be acquired from diet
- Linoleic acid is the parent omega-6 (n-6) fatty acid
  - Precursor to arachidonic acid
- α-linolenic acid is the parent omega-3 (n-3) fatty acid
  - Precursor to eicosapentaenoic acid and docosahexaenoic acid


Linoleic acid (18:2 $\Delta^{9,12}$)


α-linolenic acid (18:3 $\Delta^{9,12,15}$)

Omega-3 Fatty Acids & Inflammation



Study Objective

- The purpose of this study was to investigate the relationship between inflammation and outcome in biopsy negative controls and prostate cancer cases as well as the modification of that relationship by omega-3 fatty acids.

Study Design & Methods

Study Design

- Prospective cohort study based on baseline data from a case-control study
- Secondary analysis of The Diet and Prostate Cancer (DPC) Study
  - Case-control study conducted at the Portland Veteran Affairs Medical Center (PVAMC) from December 2001 through August 2006
- Subjects
  - 240 biopsy negative controls
  - 121 prostate cancer cases

Methods: Tissue & Plasma Analysis

- Prostate tissue analysis
  - Inflammation measured by IHC on biopsy tissue from biopsy negative controls
- Plasma analysis
  - Inflammatory markers: IL-6 and CRP
    - Interleukin-6 analyzed using ELISA
    - C-reactive protein analyzed using Immulite
  - Erythrocyte fatty acid analysis (ALA, DHA, EPA)
    - Expressed as % of total fatty acids
    - Conducted using GC/MS

Methods: Outcome Data

- Assessment of outcome
  - Collected from the DPC longitudinal database and PVAMC CPRS charting system
- Outcome of interest
  - Incident prostate cancer in biopsy negative controls
  - Biochemical recurrence after localized treatment in prostate cancer cases

Stratification by Gleason Score

- Gleason score (GS)
  - Grading system for prostate cancer based on microscopic inspection of the malignant tissue
  - Sum of the most and second dominant Gleason pattern
  - Ranges from 2-10, with 10 being the most aggressive
- GS used to define low-grade and high-grade cancer for this study

Results: Descriptive Statistics

- Relatively homogenous population
  - Significant difference in education, age-adjusted Charlson score, and prostate volume at the time of initial biopsy
- No significant difference in n-3 fatty acids or plasma inflammatory markers between controls and cancer cases
  - ALA significantly lower in low-grade cancer cases compared to controls
  - IL-6 significantly higher in high-grade cancer cases compared to controls

Results: Correlations between Plasma Markers of Inflammation & N-3 Fatty Acids

Correlations after Stratification by Cancer Status

Table 5. Pearson's correlation coefficients o plasma markers of inflammation and erythrocyte fatty acids in biopsy negative controls*

	IL-6	CRP
IL-6		
CRP	0.471[a]	
ALA	0.015	0.080
DHA	-0.149[b]	-0.246[d]
EPA	-0.137[c]	-0.112

[a]p <0.001, [b]p = 0.021, [c]p = 0.034, [d]p <0.001
*IL-6, CRP, ALA, DHA, EPA were logarithmically transformed

Biopsy Negative Controls

Table 6. Pearson's correlation coefficients of plasma markers of inflammation and erythrocyte fatty acids in cancer cases*

	IL-6	CRP
IL-6		
CRP	0.252[a]	
ALA	-0.031	-0.031
DHA	0.016	-0.025
EPA	-0.061	-0.026

[a]p <0.005
*IL-6, CRP, ALA, DHA, EPA were logarithmically transformed

Prostate Cancer Cases

Results: Inflammation, N-3 Fatty Acids, and Prostate Cancer Risk

Inflammation, N-3 Fatty Acids, & Prostate Cancer Risk

- In men with CRP levels in the middle category:
  - Significant increased risk of prostate cancer with lower levels of ALA
  - Significant increased risk of prostate cancer with higher levels of DHA
  - Significant decreased risk of high-grade prostate cancer with lower levels of DHA

Results: Patient Outcome

Outcome for Biopsy Negative Controls

Table 11. Incident of prostate cancer and mortality in biopsy negative controls as of June 1, 2008.

Outcome [a]	Controls (n = 240) n (%)
Had Repeat Biopsies	99 (41.3)
Developed Prostate Cancer [b]	17 (7.1)
Deceased	10 (4.0)

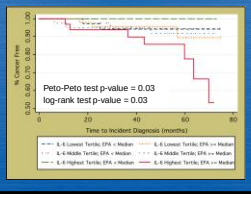
[a] Median follow-up time in months (range): 51.5 (3.0 - 78.0)
[b] Includes subject who developed prostate cancer before June 1, 2008 and no less than 6 months after their initial biopsy

- Median follow-up time was 51.5 months
- Median time to incident of prostate cancer was 27 months

Results: Inflammation, N-3 Fatty Acids, & Prostate Carcinogenesis

Inflammation, N-3 Fatty Acids, & Prostate Carcinogenesis

- Significant increased risk of developing prostate cancer in men with higher levels of EPA
- Significant increased risk also observed in men with higher levels of EPA and increasing levels of CRP



Results: Systemic Inflammation & Prostate Tissue Inflammation

Systemic Inflammation & Prostate Tissue Inflammation

Table 14. IL-6 and CRP plasma levels in biopsy negative controls with and without prostate tissue inflammation at the time of initial biopsy

	Prostate Tissue Inflammation		
	Present (n = 114)	Not Present (n = 126)	*p*[a]
	median (range)		
IL-6 (pg/mL)	1.99 (0.54 - 26.3)	1.69 (0.64 - 22.7)	0.038
CRP (mg/L)	1.70 (<0.3 - 29.6)	1.20 (<0.3 - 42.6)	0.047

[a] Wilcoxon rank sum test

Systemic Inflammation & Prostate Tissue Inflammation

Table 15. Odds of prostate tissue inflammation in biopsy negative controls

	Age-adjusted		
	No. with inflammation/ no. without inflammation (114/126)	Odds Ratio	95% Confidence Interval
IL-6 (pg/mL)			
< 1.50	26/54	1.00	Referent
1.50 < 2.33	44/35	2.61*	1.37, 4.97
³ 2.33	44/35	2.46*	1.29, 4.70
p*Trend*		*0.007*	
p*Effect*		*0.004*	
CRP (mg/L)			
< 3	86/100	1.00	Referent
3 < 10	19/20	1.1	0.55, 2.20
³ 10	9/6	1.74	0.59, 5.13
p*Trend*		*0.35*	
p*Effect*		*0.59*	

* Significantly different from reference group (Wald Test p-value = 0.004)
* Significantly different from reference group (Wald Test p-value = 0.006)

Discussion

- Inverse relationship between systemic inflammation and n-3 fatty acids (DHA & EPA) was only observed in men without prostate cancer
  - Why?
- Cancer may causes cellular changes
  - Membrane fatty acid composition
  - Enzyme function
  - Metabolic pathways

Discussion

- Relationship between n-3 fatty acids and prostate cancer risk has not been consistently described by previous research
- Possible reasons for discrepancies
  - Genetic variations
  - Relationship between n-3 and n-6 fatty acids
  - Dietary levels of n-3 fatty acids

Conclusions

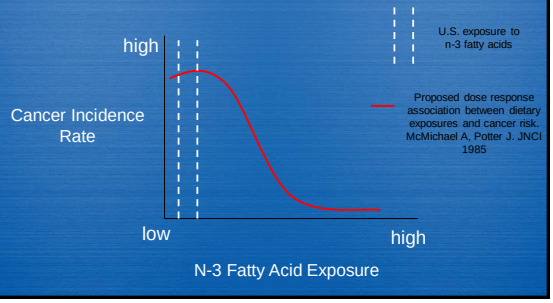
- Higher intakes of n-3 fatty acids may reduce systemic inflammation in men without prostate cancer
- Systemic inflammation may indicate inflammation in the prostate
  - More research needed to validate these results
- Further research focused on the relationship between n-3 fatty acids and prostate cancer is needed
  - Research should be conducted in populations with adequate DHA and EPA levels or in conjunction with supplementation

Questions

Dietary Recommendations

- Dietary Reference Intake
  - ALA
    - 1.1 g/day for women
    - 1.6 g/day for men
- American Heart Association
  - Normal adults
    - Consume fish 2x/week
  - Adults with CHD
    - 1 g/day EPA+DHA
  - Adults with elevated triglycerides
    - 2 - 4 g/day EPA+DHA

Dietary Exposures & Cancer Risk



N-3 Fatty Acid Exposure

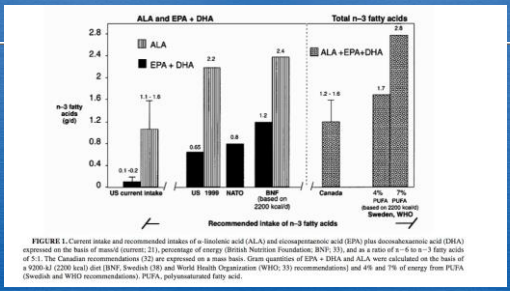


FIGURE 1. Current intake and recommended intakes of α-linolenic acid (ALA) and eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) expressed on the basis of mass/d (current; 21), percentage of energy (British Nutrition Foundation; BNF; 33), and as a ratio of n−6 to n−3 fatty acids of 5:1. The Canadian recommendations (32) are expressed on a mass basis. Gram quantities of EPA + DHA and ALA were calculated on the basis of a 9200-kJ (2200 kcal) diet [BNF, Swedish (38) and World Health Organization (WHO; 33) recommendations] and 4% and 7% of energy from PUFA (Swedish and WHO recommendations). PUFA, polyunsaturated fatty acid.