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

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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
**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**

- 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
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

<table>
<thead>
<tr>
<th></th>
<th>Biopsy Negative Controls</th>
<th>Prostate Cancer Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6</td>
<td>CRP</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>0.471*</td>
<td>0.252*</td>
</tr>
<tr>
<td>ALA</td>
<td>0.015</td>
<td>-0.031</td>
</tr>
<tr>
<td>DHA</td>
<td>-0.149*</td>
<td>0.016</td>
</tr>
<tr>
<td>EPA</td>
<td>-0.133*</td>
<td>-0.061</td>
</tr>
</tbody>
</table>

Results: 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

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

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Controls (n = 240)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Had Repeat Biopsies</td>
<td>99 (41.3)</td>
<td></td>
</tr>
<tr>
<td>Developed Prostate Cancer</td>
<td>17 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Deceased</td>
<td>10 (4.0)</td>
<td></td>
</tr>
</tbody>
</table>

*Table includes subject who developed prostate cancer before June 1, 2008 and no less than 6 months after their initial biopsy.*

Results: 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

<table>
<thead>
<tr>
<th>Prostate Tissue Inflammation</th>
<th>Present (n = 114)</th>
<th>Not Present (n = 126)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6 (pg/mL)</td>
<td>1.99 (0.54 - 26.3)</td>
<td>1.69 (0.64 - 22.7)</td>
<td>0.038</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>1.70 (0.39 - 29.6)</td>
<td>1.20 (0.39 - 42.6)</td>
<td>0.047</td>
</tr>
</tbody>
</table>

*Wilcoxon rank sum test*
**Systemic Inflammation & Prostate Tissue Inflammation**

<table>
<thead>
<tr>
<th>IL-6 (pg/mL)</th>
<th>No. with inflammation/ no. without inflammation</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.50</td>
<td>26/54</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>1.50 - 2.33</td>
<td>46/20</td>
<td>2.61</td>
<td>1.07 - 5.99</td>
</tr>
<tr>
<td>&gt; 2.33</td>
<td>44/35</td>
<td>2.48</td>
<td>1.29 - 4.70</td>
</tr>
</tbody>
</table>

**CRP (mg/L)**

<table>
<thead>
<tr>
<th>CRP (mg/L)</th>
<th>No. with inflammation/ no. without inflammation</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3</td>
<td>86/100</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>3 - 10</td>
<td>19/20</td>
<td>1.15</td>
<td>0.50 - 2.20</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>6/6</td>
<td>3.69</td>
<td>1.59 - 6.73</td>
</tr>
</tbody>
</table>

**Discussion**

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

**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 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

Cancer Incidence Rate

N-3 Fatty Acid Exposure

U.S. exposure to n-3 fatty acids

Proposed dose response association between dietary exposures and cancer risk.

McMichael A, Potter J. JNCI. 1985

Proposed dose response association between dietary exposures and cancer risk.

McMichael A, Potter J. JNCI. 1985

Recommended intake of n-3 fatty acids

ALA and EPA + DHA

Total n-3 fatty acids

ALA and EPA + DHA

Total n-3 fatty acids

ALA and EPA + DHA

Total n-3 fatty acids

ALA and EPA + DHA

Total n-3 fatty acids

ALA and EPA + DHA

Total n-3 fatty acids