

The Impact of Flaxseed on Prostate Cancer

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Flaxseed: Enreco, Inc

What is Flaxseed?



- Oilseed/grain consumed prevalently in the Middle Ages

Why Flaxseed?

Richest source of lignans (800x more than other foods)

- affects androgen metabolism (enterohepatic binding of testosterone, increases sex hormone binding globulin, reduces 5 α reductase)
- general antimitotic, antiangiogenic, antioxidant & estrogenic effects

Richest source of plant-based omega-3 (ω -3) fatty acids

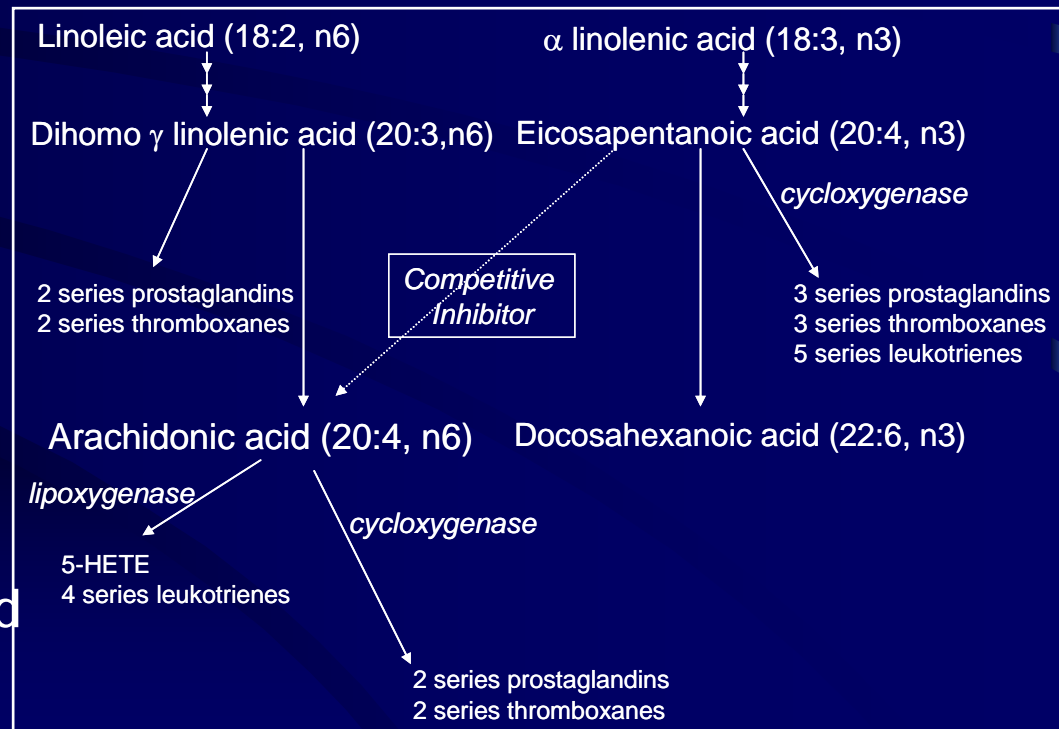
- inhibits cell membrane synthesis & alters cell membranes (receptors)
- inhibits protein kinase C/ tyrosine kinases
- increases natural killer cells
- affects the eicosanoid milieu

Why a Low Fat Diet?

Reduce ω -6 fatty acids

Previous studies suggest that low fat diets may hinder prostate cancer

Our pilot studies used flaxseed & a low fat diet together & had favorable effects



Phase II Randomized Controlled Trial Flaxseed Supplementation &/or Dietary Fat Restriction in Men with Prostate Cancer Presurgery R01 CA85740

1090 Prostate Cancer Cases Screened

Consented – Collection of Baseline blood, urine, seminal fluid & survey data

929 Excluded

447 Ineligible
354 Refusals
108 No response
3 Unusable address
17 Other

161
Randomized

Stratified on Gleason sum (<7 vs. 7+) & race (black vs. non-black)

Control
(n=41)

Usual diet

**Flaxseed
Supplementation**
(n=40)

30 g. ground flaxseed/day

Low Fat Diet
(n=40)

<20% of energy from fat

**Flaxseed + Low
Fat** (n=40)

30 g. ground flaxseed/day +
<20% of energy from fat

2 Lost-to-Follow-up

1 Lost-to-Follow-up

5 Lost-to-Follow-up

4 Lost-to-Follow-up

Before Surgery: Collection of blood, urine, seminal fluid & survey data
After Surgery: Collection of prostatic tissue

41 Included in
Intention-to-Treat
Analysis

40 Included in
Intention-to-Treat
Analysis

40 Included in
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Analysis

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Eligibility Criteria

- **men with pathologically confirmed PC who elected prostatectomy as their primary treatment**
- **at least 21 days away from their scheduled surgery**
- **mentally-competent**
- **English-speaking and -writing**
- **telephone access**
- **Not routinely consuming flaxseed and/or a diet low in fat**
- **Antibiotic-use within the 21-day study period**
- **No neoadjuvant therapy**
- **No newly-started supplement-use (within 3 months) or planned supplement-use.**

Measures & Measurement Points

Measures	Baseline	Study End
Histopathological Endpoints		
Proliferation Rate (MIB-1) PRIMARY ENDPOINT	-	X
Apoptosis (TUNEL)	-	X
Serologic Endpoint (Total PSA)	X	X
Hormone-Related Mediators		
Total Testosterone, Free Androgen Index (SHBG), IGF1, IGFBP3	X	X
Nutritional Biomarkers		
Lignans in Ejaculate (controlled for zinc)	X	X
Urinary Lignans	X	X
Erythrocyte Fatty Acid Profiles	X	X
Prostate Tissue Fatty Acid Profiles	-	-
Other Endpts, Markers of Adherence, Confounders		
Total and LDL Cholesterol	X	X
Food Frequency (DHQ)	X	X
Physical Activity (Cooper Questionnaire)	X	X
Body Weight	X	X
Side Effects (CALGB Toxicity Index)	-	X

Characteristics of the study sample (n=161)

		Total
<u>Age (years)</u>	Mean (sd)	59.2 (7.3)
	Range	36-73
<u>Race % (N)</u>	White	70%
	African American	26%
	Other	4%
<u>Education % (N)</u>	<High School	9%
	High School Grad/GED	20%
	Some College/Trade	29%
	College Grad/Post-grad	42%
<u>Biopsy Gleason Sum</u>	<7	68%
	7+	32%

Days on Protocol, Side Effects & Self-Rated Adherence

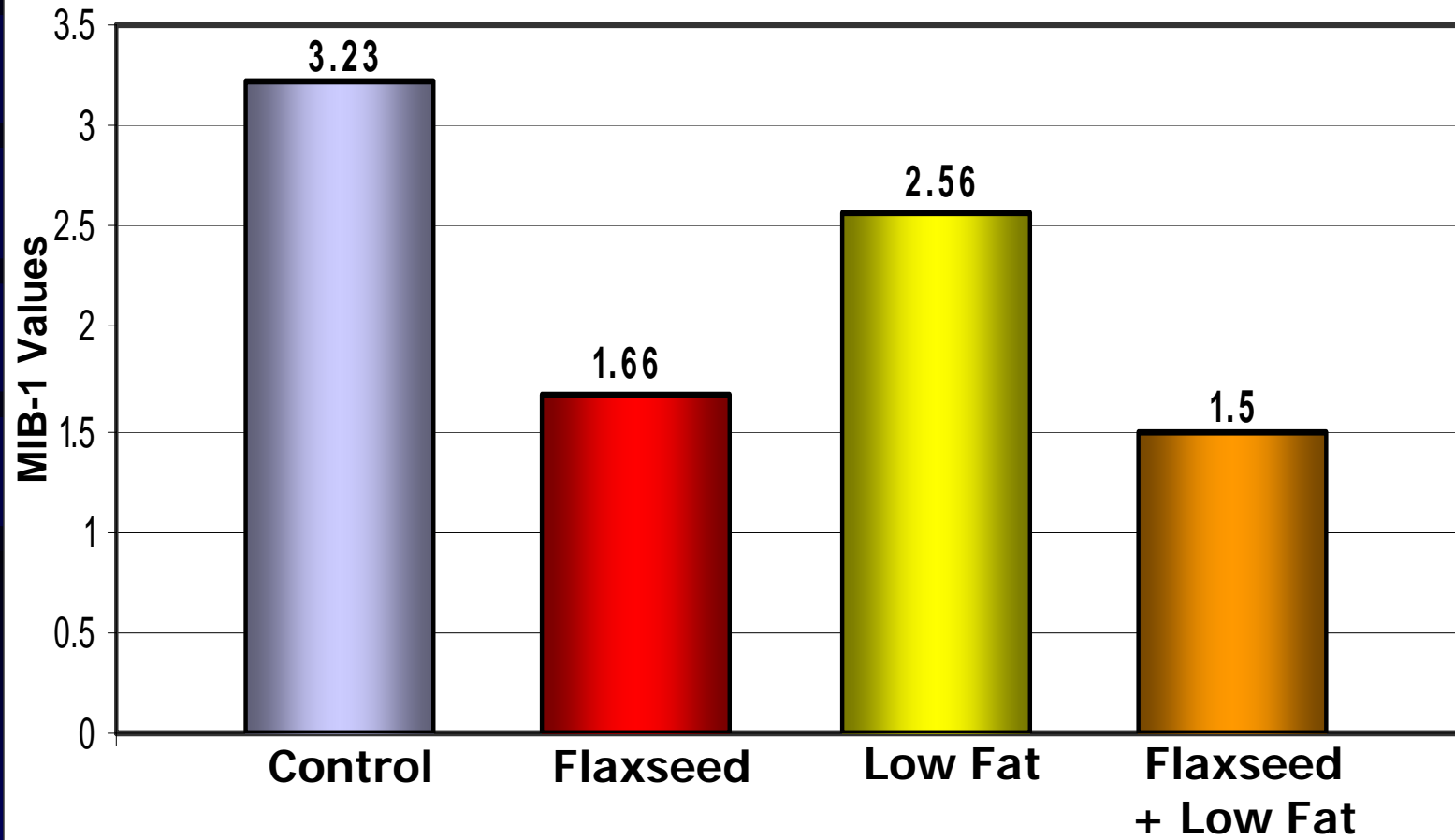
	Control (n=41)	Flaxseed (n=40)	Low Fat (n=40)	FS + LF (n=40)
# of Days on Protocol	30	31	31	30
Days/Week Adherent	-	6.9	6.5	6.8/6.3
Side Effects (% grades (1/2/3))				
nausea	7/0/0	5/0/0	21/2/0	8/0/0
vomiting	0/0/0	0/0/0	0/0/0	0/0/0
diarrhea	5/2/0	17/0/0	0/0/0	13/0/0
impotence	15/5/10	8/2/7	24/0/5	11/3/8
allergy	0/2/0	0/0/0	0/0/0	0/1/0

No significant differences between arms for all measures

Change Scores for Nutrient Intake & Nutritional Biomarkers

	Control	Flaxseed	Low Fat	FS + LF	P-values	
	(n=41)	(n=40)	(n=40)	(n=40)	FS	LF
Dietary Lignan $\mu\text{g}/\text{day}$ Δ	+3.8	+258129	+9.5	+253152	<.0001	NS
Urinary Lignan (ng/mg creatinine) – Δ	+78	+18467	+230	+13267	<.0001	NS
Seminal Fluid Lignan ($\mu\text{g}/\text{ml}$)– Δ	+93	+198	-2	+237	.013	NS
% Dietary Fat – Δ	-1%	-1%	-8%	-10%	NS	.0001
Diet ALA (mg/day)– Δ	+0.2	+31	-1	+35	<.0001	NS
Diet EPA (mg/day) – Δ	0	0	+0.1	+0.2	NS	.003
Diet $\omega 3/\omega 6$ – Δ	0	+0.43	+0.01	+0.62	<.0001	NS
Prostatic ALA (% FA)	.07	.36	.07	.09	NS	NS
Prostatic EPA (% FA)	.27	.32	.22	.37	.01	NS
Prostatic $\omega 3/\omega 6$.44	.91	.50	.78	.0001	NS

Primary Endpoint: Median Tumor Proliferation Rates



Wilcoxon 2-sided $p=0.0013$ for flaxseed/ $p=0.53$ for low fat

Other Outcomes

	Control (n=41)	Flaxseed (n=40)	Low Fat (n=40)	FS + LF (n=40)	P-values	
					FS	LF
Apoptosis (TUNEL) 0	84%	74%	74%	89%	NS	NS
> 0-1	13%	16%	14%	3%		
> 1-2	3%	10%	12%	8%		
PSA (ng/ml) - Δ	-0.61	-0.07	-0.30	-0.18	NS	NS
Testosterone (ng/dL)- Δ	-48	-39	-52	-8	NS	NS
SHBG (nmol/L)	-1.9	-1.6	-0.2	+0.8	NS	NS
Free Androgen Index	-0.7	-0.3	-1.8	-0.7	NS	NS
IGF-1 (ng/ml)	-6	-7	-3	-1	NS	NS
IGFBP-3 (mg/L)	-0.3	-0.3	-0.4	-0.3	NS	NS
Cholesterol (mg/dL)	+9	-26	-46	-37	NS	.048
CRP(mg/L)	+2.3	+4.8	+0.9	-0.2	NS	NS

Conclusions

- Both the low fat diet & flaxseed supplementation were well-accepted & well-tolerated.
- Prostate cancer proliferation rates were significant lower in men assigned to flaxseed supplementation.
- Other biomarkers associated with prostate cancer (apoptosis, androgen metabolism, IGF-1/IGFBP-3) were not significantly affected.
- Serum cholesterol was significantly reduced in men assigned to the low fat diet.
- Further study is needed to...
 - validate findings using the presurgical model
 - determine effects using other models, e.g. after biochemical failure
 - disentangle potential synergies between the low fat diet & flaxseed supplementation and if effects are due to lignan or to fat
 - determine potential mechanisms

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