The Potential of Omega-3 Fatty Acid Supplements to Improve Outcomes in Obese Breast Cancer Patients
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Declaración de Intereses:

No financial disclosure
No off label use

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I am not a nutritionist
I don’t speak Spanish
Obesity is a WORLD WIDE Epidemic
The Obesity – Cancer Connection
How Does Obesity Impact the Essential Aberrations in Cancer?

- Dysregulated growth signals and cellular energetics
- Inflammation
- Genomic instability
- Tissue invasion and metastasis
- Sustained angiogenesis
- Limitless replicative potential
- Evading growth suppression, apoptosis, and immune surveillance
13 cancers are associated with overweight and obesity
Obesity and Breast Cancer

Obesity is associated with a worse breast cancer prognosis:

- Increased metastatic recurrence
- Decreased disease-free interval and overall survival
- Strongest association seen in postmenopausal, ER\(\alpha\) positive breast cancers
Polyunsaturated Fatty Acid (PUFA) Intake and Cancer Prevention and Treatment
N-3 and N-6 Fatty Acids in Breast Adipose Tissue and Relative Risk of Breast Cancer in a Case-Control Study in Tours, France

Virginie Maillard, Philippe Bougnoux, Pietro Ferrari, Marie-Lise Jourdan, Michelle Pinault, Flore Lavillonnière, Gilles Body, Olivier Le Floch, Véronique Chajès

• case-control study

• examined the fatty acid composition in adipose tissue from:
  • 241 patients with invasive, nonmetastatic breast carcinoma and
  • 88 patients with benign breast disease

• Individual fatty acids were measured as a percentage of total fatty acids

• Unconditional logistic regression modeling was used to obtain odds ratio estimates while adjusting for age, height, menopausal status and body mass index

• Significant inverse correlation between breast cancer risk and high ratio of omega-3 to omega 6 FA
Mechanisms by Which PUFAs Modulate Tumorigenesis/Treatment Response

• Activation/Suppression of signal transduction pathways
  • PI3K/Akt pathway
  • and/or mTOR pathway

• Regulation of gene expression – i.e. PPARγ activation

• Modulation of inflammation – i.e. COX2 pathway
The Obese Tumor Microenvironment

Breast Cancer Cells
- ↑ ERα activity
- ↑ Estradiol
- ↑ Aromatase
- ↑COX-2 → ↑PGE2

Pre-adipocytes
- ↑ Estradiol
- ↑ Aromatase

Obesity-Associated Systemic Factors
- ↑COX-2 → ↑PGE2

Macrophages
NSAID use attenuates breast cancer recurrence in overweight and obese women: Role of prostaglandin-aromatase interactions

Daily NSAID use associated with \textit{48\% lower recurrence rate on hormone therapy} in a predominantly overweight/obese ER+ breast cancer patient population

Time to recurrence \textit{delayed by 28 months}
A Phase 0, Investigator Initiated Study, Evaluating the Impact of COX2 Inhibition on Human Sera Biomarkers from Obese Subjects – Pilot study funded by the Mays Cancer Center/UTHSCSA

- Prospective, comparative, short term (29 day), non-interventional study with correlative biomarker endpoints
- 120 subjects randomized assignment to 3 arms
  a. ASA 81mg po daily
  b. 1500mg of docosahexaenoic acid (DHA) and 2500mg eicosapentanoic acid (EPA) given daily
  c. Combined ASA and DHA/EPA at above doses
30 Day Omega-3 PUFA Supplementation Correlate With Decreased Serum PGE2 Levels

- Average non-obese BMI: 25.0
- Average obese BMI: 35.7

- PGE2 levels:
  - Non-obese median: 213.35
  - Obese Pre-median: 264.63
  - **Obese Post-median: 217.07**

Forty obese postmenopausal women were given 1500 mg DHA and 2500 mg EPA daily for 30 days. Serum samples were collected prior to and on day 29 and PGE2 levels assessed by ELISA.
Omega-3 Fatty Acid Modulation of Obesity-Induced Aromatase Expression – funded by the NCI/NIH

- Prospective, comparative, three arm, short term, non-interventional study with correlative biomarker endpoints.
- 60 obese (≥ 30 BMI) newly diagnosed ER+ postmenopausal breast cancer patients
- Short term (30 day) Phase 0 biomarker evaluation study prior to surgical resection.
- Patients will be randomized to three arms of 20 patients each –
  - Letrozole 2.5 mg by mouth/daily
  - Omega-3 FFAs (2000mg by mouth twice daily)
  - A combination of the two.
Local Aromatase Expression Correlates with BMI Status

(n= 45, 2 samples still missing BMI)
Local Aromatase Expression Decreases After 30 Day Omega-3 PUFA Supplementation

After 30 days, the average circulating levels of:

- omega-3 PUFAs (DHA + EPA) to omega-6 PUFAs (AA) increased by more than 4-fold
- PGE2 levels decreased by 10%

Local aromatase expression was decreased
Summary of Results

- Obesity rates are at epidemic levels worldwide.
- Obesity increases breast cancer progression/metastases and is associated with decreased response to hormone therapy and induction of local aromatase expression.
- Suppression of inflammation improves breast cancer outcomes.
- Daily supplementation with omega-3 fatty acids decreases circulating PGE2 levels in obese postmenopausal women.
- Suppression of PGE2 signaling correlates with decreased local breast aromatase expression.

Increasing omega-3 PUFA intake may provide clinical benefit to postmenopausal breast cancer patients on hormone therapy.
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