Inflammation and Cancer: the role of diet

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Inflammation

- A pathophysiological state characterized by leukocytic infiltration and cytokine secretion
- A precursor of coronary heart disease, hypertension, type 2 diabetes, Alzheimer disease, and many types of cancer
- Measured in clinical trials by circulating levels:
  - hs-CRP (high sensitivity C-reactive protein)
  - TNF-a (tumor necrosis factor alpha)
  - IL-6 (interleukin 6)
Ancient Association of Cancer with Inflammation

- Cancer is derived from Greek for crab
- Hippocrates: used the term *karkinos* to describe inflammatory breast tumors in which dilated superficial veins resembled the claws of a crab.
- Claudius Galenus: similarity between cancerous tissue and inflamed tissue.
Modern Association of Cancer and Inflammation

- Virchow (1863): leukocytic infiltration in neoplastic tissue reflected the origin of cancer at sites of chronic inflammation.
- Dvorak (1986): cancer and inflammation share angiogenesis and infiltrating leukocytes and called cancers “wounds that do not heal”.
Aspirin and NSAID Use Protects Against Cancer (except Renal)

- Colon: Ann Int Med 2007; 17,871-889
- Breast: JNCI 2008;100,1439-1447
How Chronic Inflammation Promotes Carcinogenesis

- Induces DNA instability and mutation
- Promotes angiogenesis
- Creates a tumor-promoting environment
  - Cytokines
  - Chemokines
  - Growth factors
  - Proteases
“Although cancer is a disease caused by mutations in various genes, the component that seems to be required for the mutated cells to survive, proliferate and migrate is chronic inflammation”

○ Aggarwal, MD Anderson Cancer Center

TNF $\rightarrow$ NFkB $\rightarrow$ IL6 and STAT3, which promote cell migration and metastasis.
Contrast: Acute Inflammation May Kill Tumor Cells

- Bruns (1868): regression of cancer with bacterial infection.
- Coley (1891): extracts of gram negative bacteria induce tumor regression.
- Shear (1944): bacterial LPS stimulate macrophage TNF production.
  - TNF may induce or inhibit apoptosis
The TNF/NFkB Quandry
(Agarwal & Sung, Oncology 2011)

- TNF induces apoptosis in some cancer cells but it induces growth in others.
- TNF expressed by immune cells is therapeutic.
- TNF expressed outside the immune system is pathologic.
- Acute inflammation kills cancer cells, chronic inflammation promotes them.
Activated NFkB is found in almost all types of tumors and may be required for tumor cell survival.

Radiation and most types of cancer chemotherapy paradoxically activate NFkB.

How to control NFkB activation? Will an anti-inflammatory diet help?
Dietary Effects on Chronic Inflammation

- Glycemic index
- Fiber
- Fatty acid composition
- Carotenoid content
- Flavonoid content
- Magnesium consumption
- Dietary pattern

Saturated Fatty Acids (SFA) May Promote Inflammation

- NHANES 99-00: SFA in serum phospholipids positively correlated with hs-CRP and fibrinogen
- India, young adults (Nutrition. 2006;22:865-71): dietary SFA increases hs-CRP, continuous:
  - Each 1% decrease in energy from SFA decreases hs-CRP by 0.14 mg/L
- EPIC study: weak association of SFA and breast cancer
- NIH/AARP: moderate risk for breast and pancreatic cancer with increased SFA
Review: SFA content is a major determinant of the magnitude of postprandial inflammatory response, with high meal SFA increasing inflammatory indices [not every study shows this]

Netherlands, obese humans:
- 8 week high SFA diet (19% kcal)
- abdominal fat pad biopsies
- increased expression of adipose tissue genes promoting inflammation

van Dijk et al: *A saturated fatty acid-rich diet induces an obesity-linked proinflammatory gene expression profile in adipose tissue of subjects at risk of metabolic syndrome.* 
Dietary *trans*-Fatty Acids May Increase Inflammation

- Harvard Nurses Health Study: hs-CRP 73% higher for highest quintile of TFA compared lowest quintile. TFA increases soluble TNF-receptor 1 and 2.
- Review (Eur JCN 2009;63 S 2:S5-21): TFA increases TNF-a, IL-6, and HS-CRP
n-3 PUFA Consumption Has Anti-inflammatory Effects

- MESA: dietary n-3 PUFA and non-fried fish: inversely associated with IL-6, MMP-3  Am J Cardiol. 2009;103:1238-43.
- EPIC and Physician’s Health Studies show inverse association between fish intake and cancer risk
What Level of n3 Consumption Shows an Effect?

n-3/n-6 Ratio Is Inversely Associated with Inflammation

- ATTICA study, n3/n6 ratio had strongest inverse correlation of any parameter
- Many experimental studies demonstrate carcinogenic effects of n-6 fatty acids.
Summary: Dietary Fat and Inflammation

- SFA and TFA consumption increases markers of inflammation
- n-3 PUFA consumption decreases inflammation
- n-6 PUFA consumption may increase inflammation when n-3 levels are low
- GOAL:
  - no TFA
  - limit SFA to <10% of kcal
  - limit n-6 PUFA to <7% of kcal
  - increase n-3 PUFA’s to 1 to 2% of kcal
There Are 600 Carotenoids

- **Backbone:** 40 carbon isoprene polymers \([\text{CH}_2\text{=C(CH}_3\text{)CH=CH}_2]\) \(x8\)
- **Xanthophylls** contain oxygen
  - Lutein
  - Zeaxanthin
  - Cryptoxanthin
  - Astaxanthin
- **Carotenes** contain no oxygen
  - Alpha and beta-carotene
  - Lycopene
Dietary Carotenoids May Exert Anti-inflammatory Effects

- Women’s Health and Aging Study: lower dietary alpha- and beta-carotene, lutein/zeaxanthin, or total carotenoids predicted higher IL-6 at 2 yrs
  

- Numerous study have found an inverse relationship between dietary or tissue carotenoid content and cancer development. The effects of beta-carotene supplements in smokers are an exception.
FLAVONOIDs

BASIC STRUCTURE = FLAVONE (2-PHENYL CHROMONE)

- This basic nucleus is hydroxylated, methoxylated, glycosylated and polymerized to produce the wide array of natural plant flavonoids (over 400 types in the human diet, over 4,000 in nature)
CLASSES OF FLAVONOIDS

- Glycosides
  - rutin, hesperidin

- Aglycones
  - flavanols (quercetin, kaempferol)
  - anthocyanidins (catechin)
  - isoflavonoids (genistein, daidzein)
  - anthocyanins (malvidin, peonidin)

- Proanthocyanidins
  - dimers, trimers of anthocyanidins

- Tannins
  - polymeric anthocyanidins
U.S. population survey, consumption of flavonoids was inversely related to hs-CRP. Quercetin, kaempferol, malvidin, peonidin, daidzein, and genistein each had inverse associations with serum hs-CRP, even after adjustment for total fruit and vegetable consumption.

Flavonoid Consumption and Cancer Risk/Recurrence

- **China:** Soy isoflavones protect against breast cancer and improve survival

- **Italy:** Associations between various flavonoid classes and decreased risk of numerous cancers, except prostate
Fruit and Vegetable Consumption Combats Inflammation

Germany, healthy nonsmoking men fed 2 servings a day of fruits and vegetables for four weeks, followed by increasing fruit and vegetable consumption for another four weeks.

Those randomized to 8 fruit/vegetable servings a day had a significant decline in HS-CRP; 4 servings/day was ineffective.

Fruits, Vegetables and Cancer

- No effect in pooled studies on breast, colon or ovarian cancer
- Modest inverse association with kidney and lung cancers
- NIH/AARP: decrease in total cancer incidence in male smokers only

Reviewed in Seminar Oncol 2919; 37, 282-296.
An anti-inflammatory diet may be a good foundation diet for primary or secondary cancer prevention:

- Increase in fruits, vegetables, nuts, legumes, fish, virgin olive oil
- Aim for at least 8 servings of fruits, vegetables per day and 3 servings of fish per week
- Avoid other vegetable oils, red meat, foods made with added sugar or fat
What’s Next?

- Clinical studies on specific food components singly and in combination:
  - Curcumin
  - Genistein
  - EGCG
  - Resveratrol