Objectives

Upon completion of this course, you will be able to:
1. Provide a current definition of chronic inflammation.
2. Describe the evidence that chronic inflammation plays a role in the development & propagation of atherosclerosis, some neurodegenerative disorders and some forms of cancer.
3. Explain the impact of anti-inflammatory medications on chronic inflammation.
4. Discuss the impact of obesity and physical activity on chronic inflammation.

The Problem

- Chronic Noncommunicable Diseases (CNDs)
  - 60% of deaths worldwide
  - Cardiovascular disease
  - Breast & colorectal cancer
  - Chronic lung diseases
  - Neurodegenerative disorders
  - Insulin disorders

Acute Inflammation

- Characteristic response
  - Multiple chemical mediators released
  - "Cytokines"
    - Low molecular weight glycoproteins
  - Interferons
    - Used to fight viral infections
  - Interleukins
    - Modulate inflammatory processes

Inflammation, Atherosclerosis, Neurodegeneration and Cancer

- Acute and chronic inflammation
  - Overview of inflammatory markers
- Chronic inflammation and atherosclerosis
  - C-reactive protein and atherosclerosis
- Chronic inflammation and neurodegenerative disorders
  - Multiple sclerosis
  - Parkinson disease
  - Alzheimer disease
- Chronic inflammation and cancer risk
  - Overall, breast and colorectal cancer risk

The Problem

- Chronic Noncommunicable Diseases (CNDs)
- Acute and chronic inflammation
- Overview of inflammatory markers
- Chronic inflammation and atherosclerosis
- C-reactive protein and atherosclerosis
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  - Overall, breast and colorectal cancer risk

Brad Stockert, PT, PhD
Professor of Physical Therapy
California State University, Sacramento
Acute Inflammation

- characteristic response
  - multiple chemical mediators released
  - sources of interleukins (ILs) during acute inflammation
    - mast cells
    - macrophages
    - lymphocytes

Sequential appearance of interleukins:
- tumor necrosis factor-alpha (TNF-α)
- interleukin-1 beta (IL-1β)
- interleukin-6
- interleukin-1 receptor antagonist (IL-1ra)
- soluble tumor necrosis factor-alpha receptor (sTNF-R)

Sequential appearance of cytokines:
- interleukin-6 (IL-6)
- secreted after TNF-α & IL-1β
- secreted before IL-1ra & sTNF-R

Changes in Interleukins with Sepsis

- pro-inflammatory
  - TNF-α
  - IL-1
  - IL-6
  - sTNF-R
  - IL-1ra

- anti-inflammatory
Acute Inflammation

- characteristic response
- sequential appearance of cytokines
  - interleukin-6 (IL-6)
    - stimulates liver production & secretion
  - “acute-phase response” proteins in blood

Acute Inflammation

- characteristic response
- sequential appearance of cytokines
  - “acute-phase response” proteins in blood
    - sensitive markers of inflammation
    - erythrocyte sedimentation rate (ESR)
    - C-reactive protein (CRP)
      - CRP strongly associated with CNDs

Chronic Inflammation

- characterization in absence of acute inflammation
  - persistent 2-3 fold increase in pro-inflammatory cytokines
    - TNF-α
    - IL-6
  - persistent 2-3 fold increase in inflammatory markers
    - CRP
    - ESR

Chronic Inflammation

- characterization in absence of acute inflammation
  - 2-3 fold increase in pro-inflammatory cytokines & markers
  - advanced age (>50 y.o.)
  - obesity
  - smoking
  - atherosclerosis
  - insulin-related disorders

Endocrinology of Adipose Tissue

- Adipose tissue secretes
  - hormones
    - leptin & adiponectin
    - regulation of body weight, insulin sensitivity and fuel oxidation

Endocrinology of Adipose Tissue

- Adipose tissue secretes
  - hormones
    - leptin & adiponectin
  - “adipokines”
    - cytokines (interleukins) from adipose tissue
      - TNF-α
      - IL-6
      - CRP
Endocrinology of Adipose Tissue

- **Adipose tissue secretes: TNF-α**
  - adipose tissue is main source without acute inflammation
  - level proportional to obesity
  - level decreases with weight loss
  - level proportional to insulin resistance
  - TNF-α impairs insulin receptors

- **Adipose tissue secretes: IL-6**
  - 30% of IL-6 in nonobese individuals at rest
  - level of IL-6 elevated with obesity
  - main source of IL-6 with obesity
  - visceral fat > subcutaneous fat
  - level of IL-6 is proportional to insulin resistance
  - impairs insulin receptors
  - increases resting level of CRP

- **Adipose tissue secretes: CRP**
  - indicator of pro-inflammatory state
  - strong predictor of future problems
  - insulin-related disorders
  - vascular diseases: atherosclerosis & dementia
  - amplifies impact of other pro-inflammatory cytokines
  - suppresses fibrinolysis
  - enhances thrombus formation

- **Obese individuals**
  - obesity is strongly associated with chronic inflammation
  - elevated level of pro-inflammatory mediators & markers
  - TNF-α
  - IL-6
  - CRP
  - increased incidence vascular & insulin-related disorders
Endocrinology of Adipose Tissue

- **Obese individuals**
  - increase risk of developing
  - **vascular disorders**
    - atherosclerosis (MI, CVA, some dementias)
    - dyslipidemia
    - hypertension
    - erectile dysfunction
  - **insulin-related disorders**
    - insulin resistance
    - type II diabetes

Endocrinology of Muscle

- **Muscle tissue**
  - largest body tissue in nonobese
  - secretes hormones & interleukins when active

  - “myokines”
    - interleukins from active muscle tissue
      - IL-6
      - IL-1ra
      - sTNF-R

Endocrinology of Muscle

- **Acute exercise without injury**
  - myokines secreted: **IL-6**
    - secreted from Type I & II fibers
    - amount secreted proportional to:
      - duration & intensity of exercise
      - IL-6 may increase 100-fold with intense exercise

Endocrinology of Muscle

- **Acute exercise without injury**
  - myokines secreted: **IL-1ra** and sTNF-R
    - inhibit signal transduction
      - **IL-1ra blocks** the IL-1 receptor
      - sTNF-R **competes** with TNF-α receptor
    - block inflammatory impact of IL-1β & TNF-α

Endocrinology of Muscle

- **Acute exercise without injury**
  - no pro-inflammatory cytokines released
    - IL-1 and TNF-α are not secreted
    - systemic levels of IL-1 & TNF-α are not changed
    - IL-1ra and sTNF-R secreted from active muscle
      - inhibit signal transduction
      - action of IL-1 and TNF-α is **blocked/impaired**
Changes in Interleukins with **Sepsis**

- TNF-α
- IL-1
- IL-6
- sTNF-R
- IL-1ra

**pro-inflammatory**

**anti-inflammatory**

Changes in Interleukins with **Exercise**

- IL-6
- sTNF-R
- IL-1ra

**anti-inflammatory**

Endocrinology of Muscle

- **Acute exercise and endotoxin**
  - Endotoxin (*Escherichia coli*)
  - Physically inactive subjects injected with endotoxin
    - 2-3 fold increase in TNF-α after endotoxin
  - Physically active subjects injected with endotoxin
    - After riding stationary exercise cycle 2.5 hours
    - No increase in TNF-α following endotoxin
    - Exercise suppressed rise in TNF-α

Endocrinology of Muscle

- **Acute exercise without injury**
  - Additional myokines secreted:
    - **Interleukin-8 (IL-8)**
      - Neutrophil chemotaxis during acute inflammation
      - Stimulates local angiogenesis following exercise
      - Substantial local increase in concentration of IL-8
      - Acts in paracrine manner to stimulate local angiogenesis
    - **Interleukin-15 (IL-15)**
      - Local concentration increases with strength training
      - Local anabolic impact on muscle
      - Increase in synthesis of muscle proteins
      - Decrease in degradation of muscle proteins
      - Reduction in adipose tissue mass
**Interleukin - 6**

- absence of acute inflammation
  - nonobese individuals
    - ~30% from adipose tissue
  - obese individuals
    - majority from adipose tissue
    - level proportional to degree of obesity

- IL-6 measured at baseline & after 12 & 24 weeks of training
  - moderate intensity aerobic exercise program
- IL-6 decreased after 12 & 24 weeks of training
  - decrease in IL-6 inversely related to starting point
  - those with the highest IL-6 at start had largest decrease
- IL-6 returned to baseline after 2 weeks of detraining

**Interleukin - 6**

- absence of acute inflammation
  - IL-6 known to cause:
    - production of acute phase response proteins (CRP)
      - liver
      - adipose tissue
    - increased level of CRP
    - increased risk of behavioral/lifestyle disorders

- IL-6 is strongly associated with physical inactivity
- IL-6 decreases with chronic training
- IL-6 increases with physical inactivity

**Interleukin - 6**

- absence of acute inflammation
  - IL-6 high resting level
  - equivalent to traditional risk factors for heart disease
    - hypertension
    - hypercholesterolemia
    - physical inactivity
    - smoking

- IL-6 decreased after 12 & 24 weeks of training
  - decrease in IL-6 inversely related to starting point
  - those with the highest IL-6 at start had largest decrease
- IL-6 returned to baseline after 2 weeks of detraining

**Interleukin - 6**

- absence of acute inflammation
  - IL-6 high resting level
  - equivalent to traditional risk factors for heart disease
    - IL-6 is strongly associated with physical inactivity
    - IL-6 decreases with chronic training
    - IL-6 increases with physical inactivity

**Interleukin - 6**

- absence of acute inflammation
  - IL-6 resting level
    - decreases with chronic endurance training
      - increase in IL-6 receptor number
      - decrease in IL-6 resting level
      - increase in IL-6 sensitivity
      - decrease in risk of behavioral/lifestyle disorders

Interleukin - 6

- absence of acute inflammation
- IL-6 resting level
  - independent risk factor for future cardiovascular disorders
  - MI
  - CVA
  - dementia
  - erectile dysfunction

C-Reactive Protein (CRP)

- CRP levels at rest
  - inversely related to level of aerobic fitness
    - children and adults (obese & nonobese)
  - powerful predictor of future cardiovascular disorders
    - myocardial infarction
    - cerebrovascular accident
    - hypertension
    - diabetes

C-Reactive Protein (CRP)

- CRP levels at rest
  - marginally correlated with LDL cholesterol
  - LDL and CRP both highly correlated with future problems
  - identify different pathological processes or groups at risk
  - ~1/2 of MIs occur in people with normal LDL cholesterol

C-Reactive Protein (CRP)

- CRP levels at rest
  - statin therapy
    - Lipitor, simvastatin
    - lowers LDL cholesterol level
    - reduces CRP level
      - reduction in chronic inflammation
      - reduces risk more than reduction in LDL cholesterol
      - reduction in chronic inflammation

C-Reactive Protein (CRP)

- CRP levels at rest
  - statin therapy
  - aspirin therapy
    - given to reduce platelet adhesion
      - reduces risk of thromboembolism (MI, CVA)
    - reduces CRP level
      - reduces chronic inflammation & risk of behavioral/lifestyle disorders
      - acts synergistically with statins to reduce level of chronic inflammation
  - physical activity
    - reduces CRP level
    - independent of weight loss
    - independent of statin &/or aspirin therapy
    - aerobic and resistive exercises both work
Chronic Inflammation

- Chronic inflammation is associated with
  - physical inactivity
  - obesity
  - elevation in pro-inflammatory mediators/markers
    - TNF-α
    - IL-6
    - CRP

Chronic Inflammation

- Chronic inflammation is decreased with
  - physical activity
  - decrease in obesity
  - anti-inflammatory medications
    - each reduces level of pro-inflammatory mediators
      - TNF-α
      - IL-6
      - CRP

Chronic Inflammation

- Chronic inflammation is associated with
  - behavioral/lifestyle diseases
    - vascular diseases
      - atherosclerosis
    - MI
    - CVA
    - dementia
    - erectile dysfunction

Chronic Inflammation

- Chronic inflammation is associated with
  - behavioral/lifestyle diseases
    - vascular diseases
    - insulin-related disorders
      - insulin resistance
      - type II DM
      - metabolic syndrome

Chronic Inflammation

- Chronic inflammation is associated with
  - behavioral/lifestyle diseases
    - vascular diseases
    - insulin-related disorders
    - cancers
      - breast
      - colorectal

Chronic Inflammation

- Chronic inflammation is associated with
  - behavioral/lifestyle diseases
    - vascular disorders
    - insulin-related disorders
    - cancers
    - neurodegenerative disorders:
      - Alzheimer Disease
      - Multiple Sclerosis
Chronic Inflammation

- **Reduction in risk of behavioral/lifestyle disorders**
- changes in behavior/lifestyle
- use of anti-inflammatory medications
- *most anti-inflammatory medications have increased risk of*
  - GI distress
  - ulcers
  - adverse drug reaction
  - interaction with other medications

Inflammation & Atherosclerosis

- **Previously held view of **atherosclerosis**
  - cholesterol storage disease
  - passive deposition of lipids into arterial walls
  - continuing deposition of lipids encrusts arterial walls
  - progressing stenosis provokes occlusive thrombic event

Inflammation & Atherosclerosis

- **Current view of **atherosclerosis**
  - active process
  - arterial walls are dynamic structures
  - altered cellular behavior
  - changes mediated by molecular signals
    - cytokines

Inflammation & Atherosclerosis

- **Why doesn’t it get better over time instead of worse??**
- **Primordial role for inflammation**
  - inflammation links risk factors with lesion formation
  - inflammation *transduces* risk factors to changes in biology and cell function

Inflammation & Atherosclerosis

- **Current view of **atherosclerosis**
  - ~50% of CV deaths occur in people without hyperlipidemia
  - plaque rupture is poorly correlated with degree of stenosis
  - ~50% of infarctions occur in arteries with <50% occlusion
Inflammation & Atherosclerosis

- Current view of atherosclerosis
  - C-Reactive Protein (CRP)
    - produced during acute inflammation
    - level increases 1000-fold with acute infection
    - level remarkably stable over time without infection
    - measure of systemic inflammation
    - strong predictor of future MI & CVA

- CRP predicts risk beyond traditional risk factors
  - CRP <1 mg/l = low risk
  - CRP 1-3 mg/l = moderate risk
  - CRP >3 mg/l = high risk
  - highest vs. lowest tertile of CRP
    - 2-fold increased risk CV event with elevated CRP
    - risk elevated regardless of cholesterol level
    - TC, LDL-C & HDL-C

Inflammation & Atherosclerosis

- Physician Health Study (1997)
  - apparently health males followed for 8 years
  - CRP higher among those that suffered MI or CVA
  - CRP highest quartile vs. lowest quartile
    - 3-fold increased risk of MI
    - 2-fold increased risk of CVA
    - independent of lipid & nonlipid risk factors

- Women’s Health Study
  - Ridker PM; Lancet 2001; 358:946-947.
  - 28,263 postmenopausal women
  - monitored prospectively
  - CRP & LDL-C significant predictors of CV risk
    - CRP higher prognostic value
    - high CRP & high LDL-C 8-fold increase risk
    - CRP & LDL-C minimally correlated
    - appear to identify separate pathological groups at risk

Inflammation & Atherosclerosis

- Women’s Health Initiative
  - Pradhan AD; JAMA 2002;288:980-987.
  - prospective, case controlled study
  - 75,000 females in US initially enrolled
  - 304 developed heart disease
  - 304 case-matched controls (age, smoking, ethnicity)
  - CRP significantly elevated in those with heart disease
    - 2-fold increased risk of heart disease

Inflammation & Atherosclerosis

- Coronary angioplasty outcomes
  - CRP measured before PTCA procedure
  - assessed early & late outcomes
    - restenosis
    - complications
Inflammation & Atherosclerosis

- **Coronary Angioplasty outcomes**
  - Buffon A; J Am Coll Cardiol 1999; 34:1512-1521.
  - CRP measured before PTCA procedure
  - acute problems occurred
    - 22% of patients with high CRP
    - none in patients with normal CRP
  - one year follow-up
    - 63% with high CRP had restenosis
    - 27% with normal CRP had restenosis

- **CRP measured before PTCA procedure**
  - 22% of patients with high CRP
  - none in patients with normal CRP
  - one year follow-up
    - 63% with high CRP had restenosis
    - 27% with normal CRP had restenosis

- **Statin therapy**
  - high CRP & low LDL-C higher risk of CV event than
    - low CRP & high LDL-C
  - people with low or normal LDL-C and high CRP may benefit significantly from statin therapy

- **Statin therapy**
  - decreases recurrent events after stent placement in
    - patient with high CRP independent of LDL-C
  - survivors of MI over 5 year follow-up
    - CRP increased with standard treatment & placebo
    - statin therapy decreased CRP regardless of LDL-C
  - statin therapy associated with better clinical outcomes
    - in patient with initially higher CRP
    - Walter DH; J Am Coll Cardiol; 2001; 37:839-846

- **Aspirin therapy**
  - reduces risk of first CV event by 44%
  - several contradictory studies relating aspirin with CRP
    - few controlled for initial CRP level
    - low dosage of aspirin used
      - low dosage has anti-platelet activity
      - low dosage is not anti-inflammatory
Inflammation & Atherosclerosis

- Aspirin therapy
  - reduces risk of first CV event by 44%
  - several contradictory studies relating aspirin with CRP
  - few controlled for initial CRP level
  - low dosage of aspirin used
  - impact greatest in person with high CRP
  - largest impact on quartile with highest CRP level
  - impact declines in direct proportion to CRP level

- Summary of findings
  - Increased risk of cardiovascular event associated with:
    - elevated LDL-cholesterol
    - elevated CRP
  - Decreased risk of cardiovascular event associated with:
    - reduction in LDL-cholesterol
    - statins
    - reduction in CRP
    - statins
    - aspirin

Neurodegenerative Disorders

- Glial cells have inflammatory properties
  - glial cells can secrete:
    - TNF-α
    - IL-1β
  - TNF-α and IL-1β elevated with
    - Parkinson Disease
    - Multiple Sclerosis
    - Alzheimer Disease
    - Huntington Disease
    - ALS

- Glial-mediated inflammation
  - beneficial acutely
  - acute insults trigger compensatory neurogenesis
  - chronic inflammation inhibits neurogenesis
  - NSAIDs attenuate inflammation
    - restore neurogenesis
      - Monje ML; Science 2003; 302:1760-1765.

- Parkinson Disease
  - majority of cases are idiopathic
  - degenerative disorder of basal ganglia
    - abnormal movement pattern
  - loss of dopamine neurons in substantia nigra
    - evidence of chronic inflammation
    - microglia activity high in areas of degeneration
    - elevated TNF-α
    - elevated IL-1β
Neurodegenerative Disorders

- **Parkinson Disease**
  - majority of cases are idiopathic
  - degenerative disorder of basal ganglia
  - abnormal movement pattern
  - loss of dopamine neurons in substantia nigra
  - evidence of chronic inflammation
  - chronic NSAID use decreases risk ~45%
  - Cox-2 inhibitors reduce neuronal damage
    - demonstrated in animal models only

Neurodegenerative Disorders

- **Multiple Sclerosis**
  - demyelinating CNS disorder
  - T-cell mediated autoimmune disorder
  - chronic glial cell activation
  - elevated level of proinflammatory cytokines
    - TNF-α and IL-1β
  - spontaneous remyelination occurs
    - process is not robust
    - process is inhibited by inflammation

Neurodegenerative Disorders

- **Multiple Sclerosis**
  - detailed autopsy study
    - 67 with MS and 28 without MS
      - Frischer JM; Brain 2009; 132:1175-1189.
  - pronounced inflammation found in
    - acute and relapsing forms
    - progressive forms
    - all lesions
    - all stages of disorder
    - correlation between axonal injury & disability

Neurodegenerative Disorders

- **Multiple Sclerosis**
  - demyelinating CNS disorder
  - proinflammatory cytokines
    - TNF-α and IL-1β elevated locally
    - levels correlate with stage of disorder
Neurodegenerative Disorders

- **Multiple Sclerosis**
  - demyelinating CNS disorder
  - proinflammatory cytokines
    - TNF-α and IL-1β
  - NSAIDs impact
    - ameliorate & delay progression
    - effectiveness related to “COX-2” inhibition
  - Statins impact
    - no evidence of effectiveness

Cannabinoids impact

- anti-inflammatory properties
  - cannabidiol > THC
  - Pletcher MJ. JAMA 2012; 307:173-181
  - ameliorate progression & symptoms (rat model)

Neurodegenerative Disorders

- **Alzheimer Disease**
  - severe cognitive dysfunction
  - neurofibrillary tangles
  - amyloid plaques contain
    - activated microglia
    - inflammatory mediators
  - TNF-α and IL-1β are elevated

Neurodegenerative Disorders

- original association with inflammation
  - patients with Rheumatoid Arthritis
  - patients with heart disease
  - take high dose NSAIDs chronically
  - reduced incidence of Alzheimer Disease

Neurodegenerative Disorders

- original association with inflammation
  - clinical trials using NSAIDs
    - no benefit in some studies
    - design flaws?
      - late initiation
      - dosage used
      - no change in inflammatory markers
  - clinical trials using statins
    - may be protective
    - cross-sectional study of 3 hospital data-bases
      - incidence of AD 60% lower in patients taking statins
Neurodegenerative Disorders

- Alzheimer Disease
  - original association with inflammation
  - clinical trials using statins
    - Rotterdam study with 6992 participants
    - prospective clinical trial
    - 9 year follow-up

- Alzheimer Disease
  - original association with inflammation
  - clinical trials using statins
    - Rotterdam study with 6992 participants
    - prospective clinical trial
    - 9 year follow-up
      - statin use associated with 60% decreased incidence
      - non-statin cholesterol lowering medication
        - no effect on incidence of AD

Neurodegenerative Disorders

- Alzheimer Disease
  - original association with inflammation
  - physical activity as an intervention
    1) longitudinal study of 5925 older females
      - walking more associated with ~35% decreased risk
    2) longitudinal study of 349 adults ≥55 years of age
      - higher levels of cardiorespiratory fitness associated with
        less cognitive decline over 6 years

- Alzheimer Disease
  - original association with inflammation
  - physical activity as an intervention
    3) longitudinal study of 4615 adults
      - physical activity associated with:
        42% decrease in level of cognitive decline
        50% decrease in incidence of AD
        37% decrease in incidence of any form of dementia

Chronic Inflammation and Cancer Risk

Brad Stockert, PT, PhD
Professor of Physical Therapy
California State University, Sacramento

Cancer

- uncontrolled growth of cells
- multiple forms
- multiple causes
- multiple locations
Top 3 New Cancer Sites by Gender

- **males:**
  - prostate (25%)
  - lung/bronchus (15%)
  - colorectal (10%)

- **females:**
  - breast (27%)
  - lung/bronchus (14%)
  - colorectal (10%)

Cancer and Inflammation

- **Theodor Boveri** (1862-1915)
  - first postulated link between cancer & inflammation
  - tumorigenesis promoted by chronic inflammation
  - Several subsequent investigators & studies have shown
    - elevated CRP associated with increased cancer risk
    - association shown with many forms of cancer
      - lung, breast, rectum & prostate cancers
    - association not found with infectious cancers

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Cancer and Inflammation

- **Rotterdam study**
  - Siemes C. J Clinical Oncology 2006;24:5216-5222.
  - 7,017 participants ≥55 years of age
  - mean follow-up time = 10.2 years
  - high levels of CRP [>3mg/L]
    - compared risk vs. subject with low CRP [<1mg/L]
    - associated with increased risk of incident cancer
    - lung cancer association strongest

- **Greek study**
  - prospective study with 28,572 volunteers at start
  - 496 cancer cases
  - 996 case-matched control cases
    - matched for age, smoking, BMI and other attributes
  - CRP levels were higher in cases with cancer
    - 4.1 mg/L for cancer cases
    - 2.6 mg/L for control cases
    - association strongest for lung cancer

Cancer and Inflammation

- **Greek study**
  - prospective study with 28,572 volunteers at start
  - 496 cancer cases
  - 996 case-matched control cases
    - matched for age, smoking, BMI and other attributes

Impact of physical activity on overall cancer risk

- review of cohort & case-control studies
- occupational & recreational physical activities
- both provide protection against overall cancer risk
- graded dose-response manner
- regardless of gender
- confounding variables had little impact
**Breast Cancer and Inflammation**

- **Breast cancer**
  - excess body weight causes 20% cancer death in women ≥50 years of age in the U.S.
  - obesity is a risk factor for breast cancer
  - obese females have increased incidence of:
    - metastatic cancer at time of diagnosis
    - poorer outcome

- **Obesity**
  - weight loss is associated with decreased risk in post menopausal females
  - weight gain is associated with increased risk in pre-menopausal females

  Pichard D; Maturitas; 2008; 60: 19-30.

- **Females post menopause**
  - high estrogen levels promote breast cancer
  - adipose tissue is primary source of estrogen
  - adipose tissue is primary source of TNF-α
    - TNF-α stimulates estrogen synthesis
    - TNF-α stimulates angiogenesis
    - TNF-α is proinflammatory
  - obese females have elevated estrogen
  - obese females have higher risk of breast cancer

- **Anti-inflammatory medications**
  - aspirin inhibits cyclooxygenase activity
    - aspirin lowers prostaglandin levels
    - lowering prostaglandins reduces aromatase activity
    - lower level of estrogen observed
      - theoretically lower estrogen should translate to a lower rate of breast cancer


  - 1,581 incident breast cancers reported
  - aspirin users:
    - lower incidence of breast cancers vs. non users
      - relative risk 0.8
    - dose response relationship observed
      - aspirin use ≥5 times/week had relative risk 0.7
    - results did not vary by tumor receptor status
      - independent of hormone-receptor signaling pathway
Breast Cancer and Inflammation

- Breast cancer and anti-inflammatory medications
  - 1,581 incident breast cancers reported
- non-aspirin NSAID users:
  - no association with reduction in cancer incidence
  - no association regardless of tumor receptor status

Breast Cancer and Inflammation

- Breast cancer and anti-inflammatory medications
  - statins have anti-inflammatory properties
  - statins have other anti-cancer properties
  - response to statins varies
    - response varies by tumor type
      - breast, colorectal and prostate cancers reduced
    - response varies by type of statin used
      - lipophilic responses > hydrophilic responses

Breast Cancer and Inflammation

- Breast cancer and anti-inflammatory medications
  - statins have anti-inflammatory properties
  - statins have other anti-cancer properties
  - response to statins varies
  - statins reduce the incidence of breast cancer
    - 72% reduction in incidence
    - found with all statins

Breast Cancer and Inflammation

- Breast cancer and anti-inflammatory medications
  - statins have anti-inflammatory properties
  - statins have other anti-cancer properties
  - response to statins varies
  - statins reduce the incidence of breast cancer
    - 56% reduction in incidence
    - found with all statins

Breast Cancer and Inflammation

- Breast cancer and physical activity
  - review of 41 studies with 108,031 breast cancer cases
  - occupational & recreational physical activities
  - both provide protection against breast cancer risk
  - graded dose-response manner
    - impact higher if activity was >4.5 MET
    - impact higher with more MET-hours/week
Colon Cancer and Inflammation

- Colorectal cancer and inflammation
  - noninfectious chronic inflammation associated with:
    - increased incidence colorectal and lung cancer
  - idiopathic inflammatory bowel disease
    - colorectal cancer incidence increases over time
  - ~25% colorectal cancer cases are familial
  - most cases develop from adenomatous polyps
  - 90% of colorectal cases in patients >50 years of age

- aspirin for prevention of colorectal cancer
  -review of RCTs, case control studies and cohort studies
  - relative risk (RR) of colorectal cancer in aspirin users
    - RCT – RR = 0.82
    - case control studies – RR = 0.87
    - cohort studies – RR = 0.72

- inflammatory markers strongly associated with cancer death
  - hazard ratio for cancer death with inflammatory markers
    - 1.64 for elevated CRP
    - 1.82 for elevated TNF-α
  - elevated CRP & TNF-α strongly associated with increased incidence of lung cancer deaths
  - elevated CRP strongly associated with increased incidence of colorectal and breast cancer deaths

- CRP 25% higher in subjects with colorectal cancer
  - odds ratio was 2.9 in highest vs lowest CRP quartile
  - "dose-response" relationship observed
  - risk of colorectal cancer increased with higher CRP

- inflammatory markers strongly associated with cancer death
  - hazard ratio for cancer death with inflammatory markers
    - 1.64 for elevated CRP
    - 1.82 for elevated TNF-α
  - elevated CRP & TNF-α strongly associated with increased incidence of lung cancer deaths
  - elevated CRP strongly associated with increased incidence of colorectal and breast cancer deaths
Colon Cancer and Inflammation

• Colorectal cancer and inflammation
  • aspirin for prevention of colorectal cancer
  • prospective study of 47,363 males
    • 18 year follow-up
    • 975 cases of colorectal cancer


18 year follow-up

975 cases of colorectal cancer

Colon Cancer and Inflammation

• Colorectal cancer and inflammation
  • aspirin for prevention of colorectal cancer
  • prospective study of 47,363 males
    • determined dose-response relationship
      • 0.5 – 1.5 tablets/week – RR = 0.94
      • 2.0 – 5.0 tablets/week – RR = 0.80
      • 6.0 – 14.0 tablets/week – RR = 0.72
      • >14.0 tablets/week – RR = 0.30
    • required 6-10 years of use to show effectiveness

Prospective study of 47,363 males


Colon Cancer and Inflammation

• Colorectal cancer and inflammation
  • aspirin for prevention of colorectal cancer
  • review of 5 RCTs (14,033 subjects)
    • Rothwell PM. Lancet 2010. (published online, October, 2010)
    • primary and secondary prevention trials
    • 30-1200 mg/day
    • 20 year follow-up

Review of 5 RCTs (14,033 subjects)

Rothwell PM. Lancet 2010. (published online, October, 2010)

Colon Cancer and Inflammation

• Colorectal cancer and inflammation
  • aspirin for prevention of colorectal cancer
  • review of 5 RCTs (14,033 subjects)
    • ≥75 mg/day resulted in decreased:
      - cancer incidence
      - cancer mortality
    • benefit increased with duration of use
      - required 5+ years of use

Review of 5 RCTs (14,033 subjects)

Rothwell PM. Lancet 2010. (published online, October, 2010)

Colon Cancer and Inflammation

• Colorectal cancer and inflammation
  • aspirin for prevention of colorectal cancer
  • 2 large cohort studies analyzed
    • 82,911 females and 47,363 males
    • 22 years of follow-up
    • 636 cases of colorectal cancer

2 large cohort studies analyzed


Colon Cancer and Inflammation

• Colorectal cancer and inflammation
  • aspirin for prevention of colorectal cancer
  • 2 large cohort studies analyzed
    • 636 cases of colorectal cancer
    • 423 (67%) had moderate to strong expression of COX-2
    • 213 (33%) did not express COX-2
    • COX-2 promotes inflammation & proliferation
      over-expressed in many forms of cancers

2 large cohort studies analyzed

Colon Cancer and Inflammation

- **Colorectal cancer and inflammation**
  - aspirin for prevention of colorectal cancer
  - 2 large cohort studies analyzed
    - 636 cases of colorectal cancer
    - 423 (67%) had moderate to strong expression of COX-2
    - 213 (33%) did not express COX-2
    - 2 regular aspirin tablets/day vs COX-2 expression
      - RR = 0.64 for tumors expressing COX-2
      - RR = 0.96 for tumors not expressing COX-2

- **Statins for prevention of colorectal cancer**
  - 47% decrease in incidence of colorectal cancer
  - used statins ≥5 years
  - all statins effective

- **Impact of physical activity on colon cancer risk**
  - review of 48 studies 40,764 colon cancer cases
  - occupational & recreational physical activities
  - both provide protection against colon cancer risk
  - graded dose-response manner
  - impact higher if activity was >4.5 MET
  - impact higher with more MET-hours/week

Colon Cancer and Inflammation

- **Impact of physical activity on colon cancer risk**
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