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Dietary Targeting of Inflammation: Modification of Cancer Risk

Learning Library
TODAY'S DIETITIAN

Presented by Cynthia Thomson, PhD, RD, FAND, FTOS

Cynthia A. Thomson

PhD, RD, FAND, FTOS

- I have no disclosures to report related to this presentation.
- I serve on the Research Board for Produce for Better Health
- I serve as consulting faculty for the CDR Adult Weight Management certificate program

Learning Objectives

Suggested Learning Codes: 2110, 4040, 4050, 5150

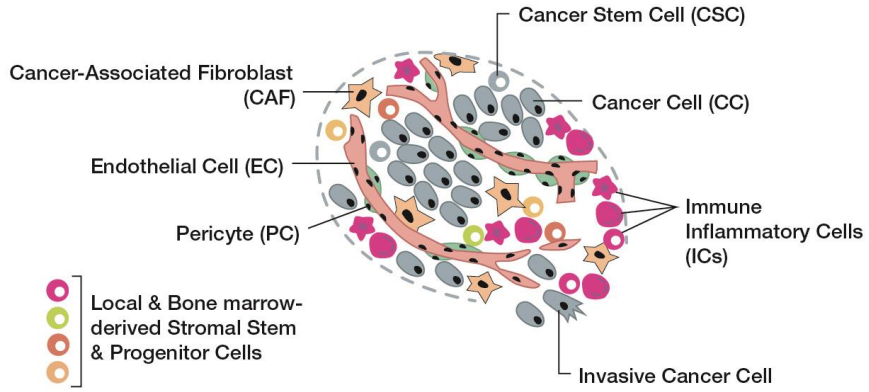
Suggested Performance Indicators: 8.1.4, 8.1.5, 8.1.3

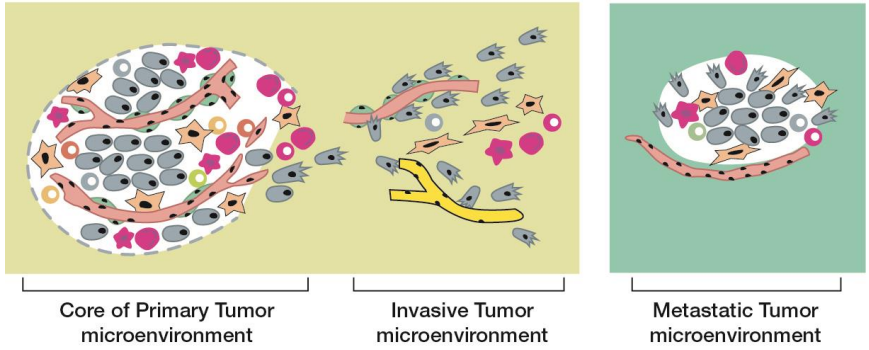
1. Describe the physiology of the relationship between inflammation and cancer.
2. Differentiate anti- and pro-inflammatory foods/dietary constituents/dietary patterns.
3. Identify common biochemical indices used to assess inflammation and their relationship to cancer and cancer prognosis.
4. Evaluate and interpret current epidemiological and clinical evidence linking inflammation, diet and cancer.
5. Translate current evidence into nutritional counseling/care plans for cancer risk reduction.

BACKGROUND

Rudolf Virchow (Father of Pathology)

- First to link of inflammation to cancer
- “Lymphoreticular infiltration” of cancer reflects the origin of cancer at sites of inflammation (1863)





Carcinogenesis

Classic Hallmarks

- Self-sufficiency in growth signals
- Insensitivity to anti-growth signals
- Inflammatory microenvironment
- Tissue invasion & metastasis
- Limitless replicative potential
- Sustained angiogenesis
- Evading apoptosis

Emerging Hallmarks

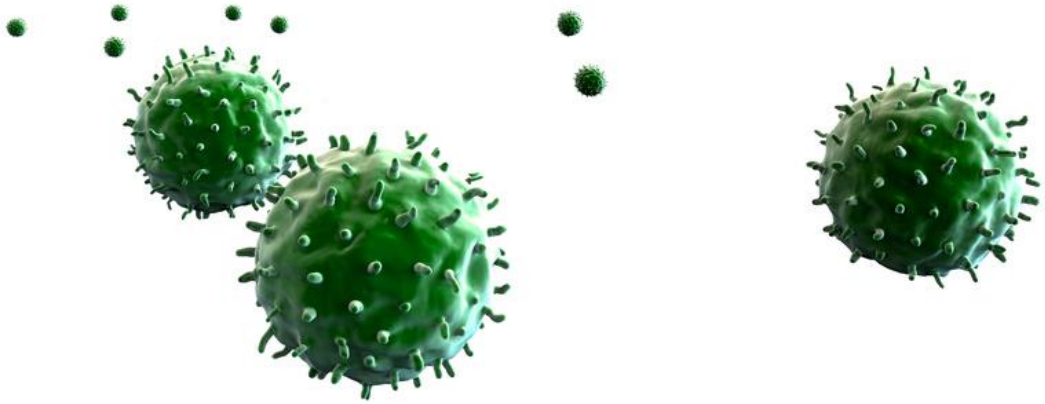
- Avoiding immune destruction
- Tumor-promoting inflammation
- Genome instability and mutation
- Deregulating cellular energetics

INFLAMMATION

Colotta F et al. Carcinogenesis, 2009.

Inflammation and the Cancer Continuum

- Chronic inflammation, Infection, Autoimmunity
- Tumor-associated inflammation
- Therapy-induced inflammation
- Inflammation caused by environmental and dietary exposure



Grivennikov et al. Cell, 2010.

Inflammatory Conditions and Tumorigenesis

Pathogenic Condition	Associated Neoplasm	Aetologic Agent
Silicosis	Lung, mesothelioma	Asbestos
Bronchitis	Lung	Tobacco
Cystitis	Bladder	Catheters
Gingivitis	Oral squamous cell	Poor dental hygiene
IBD, Crohn's, UC	Colorectal	Unknown
Chronic pancreatitis	Pancreatic	Alcoholism
Reflux esophagitis	Esophageal	Gastric acids
Skin inflammation	Melanoma	UV light

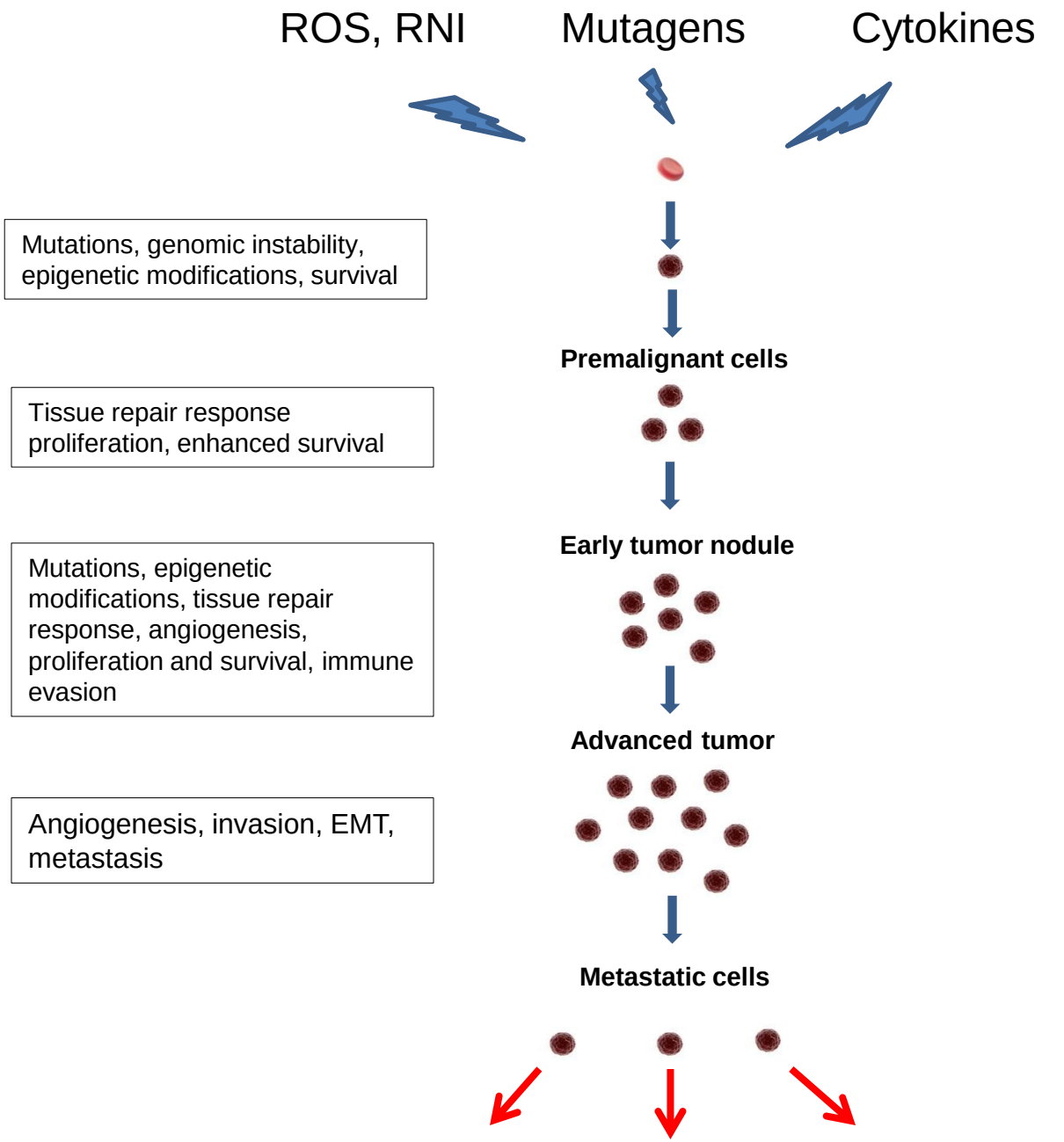
Coussens LM and Werb Z, Inflammation and Cancer, Nature, 2002

Tumorigenesis

- Tumor microenvironment assoc with oxidative stress response; cancer cells can be responsive to ER stress
- ER stress leads to migration and aggregation of immune cells with the tumor area
- In turn, tumor-promoting cytokines are stimulated and released in the surrounding tissues and systemically
- Acute-phase proteins also are activated to combat tumor growth
- As are dendritic cells which migrate to tumor in a secondary immune-centric effort to combat tumor growth

Tumorigenesis & Inflammation: Early research

- Chronic, sub-clinical inflammation may increase cancer risk
- Basic mechanistic studies in animal and cell culture models demonstrate the role of inflammatory molecules in colon tumorigenesis and metastasis
- Inflammation shown to induce reactive oxygen species and promote DNA damage (genotoxicity)
- Numerous studies reporting on regular use of aspirin and reduced risk of cancers (e.g., colorectal, ovarian, melanoma, breast)
- The inducible form of the prostaglandin-endoperoxide synthase 2 or cyclo-oxygenase 2 enzyme shown to be overexpressed in a number of cancers and to be inhibited by COX2 specific drugs (celecoxib, rofecoxib)


ROS, RNI
Mutagens
Cytokines
Mutations, genomic instability, epigenetic modifications, survival
Premalignant cells
Tissue repair response proliferation, enhanced survival
Early tumor nodule
Mutations, epigenetic modifications, tissue repair response, angiogenesis, proliferation and survival, immune evasion
Advanced tumor
Angiogenesis, invasion, EMT, metastasis
Metastatic cells

Double-Hit: Infection and Inflammation

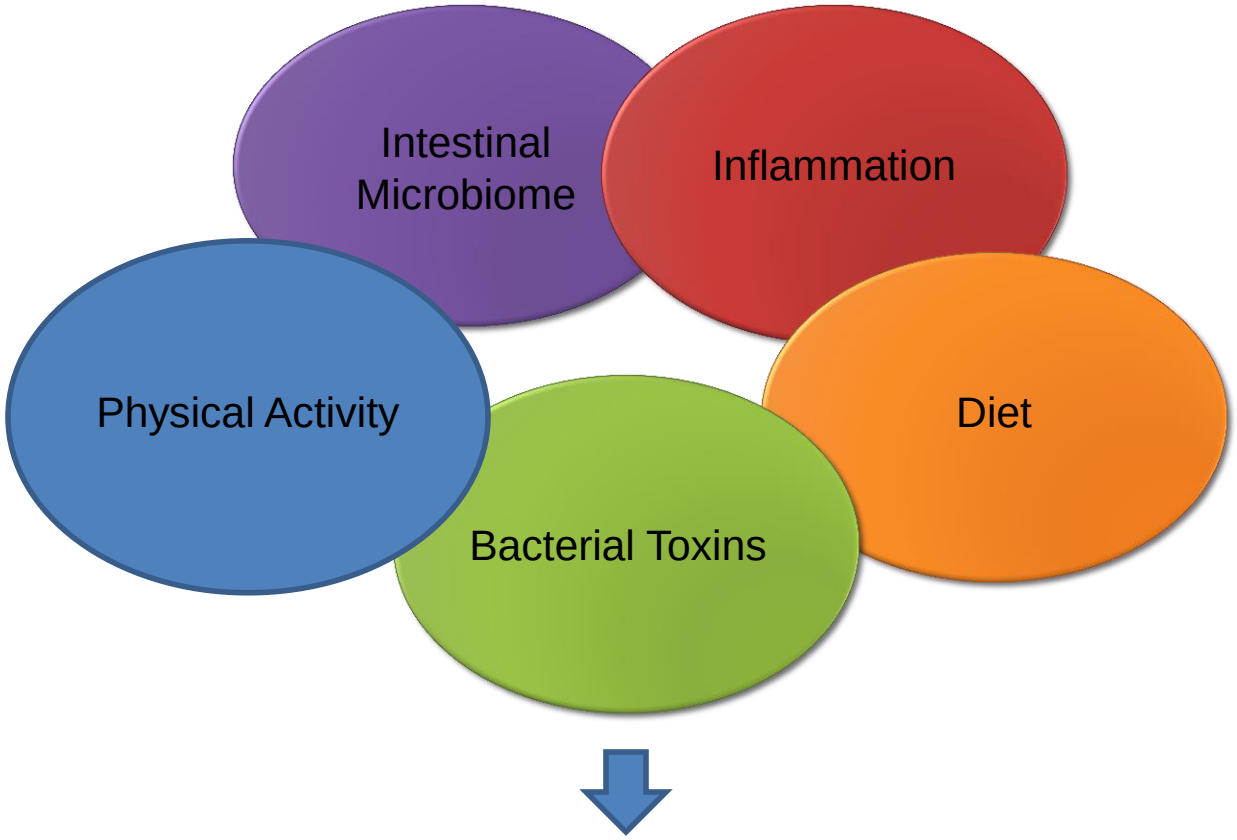
- Risk for several cancers is elevated in the presence of viruses
  - HPV- cervical
  - H pylori- gastric
  - EBV- nasopharyngeal
  - Hepatitis B, C – liver cancer
- Pathogens promote inflammation-associated immune response
- Elevated cytokines
  - Tumor growth factors
  - TSG and oncogene expression
  - Govern T-helper cell, NK cells, T regulatory cells, and Th17 cells
  - Further compounded by aging immune response

Tumor-associated Inflammation and Prognosis: Meta-analysis for Colorectal Cancer

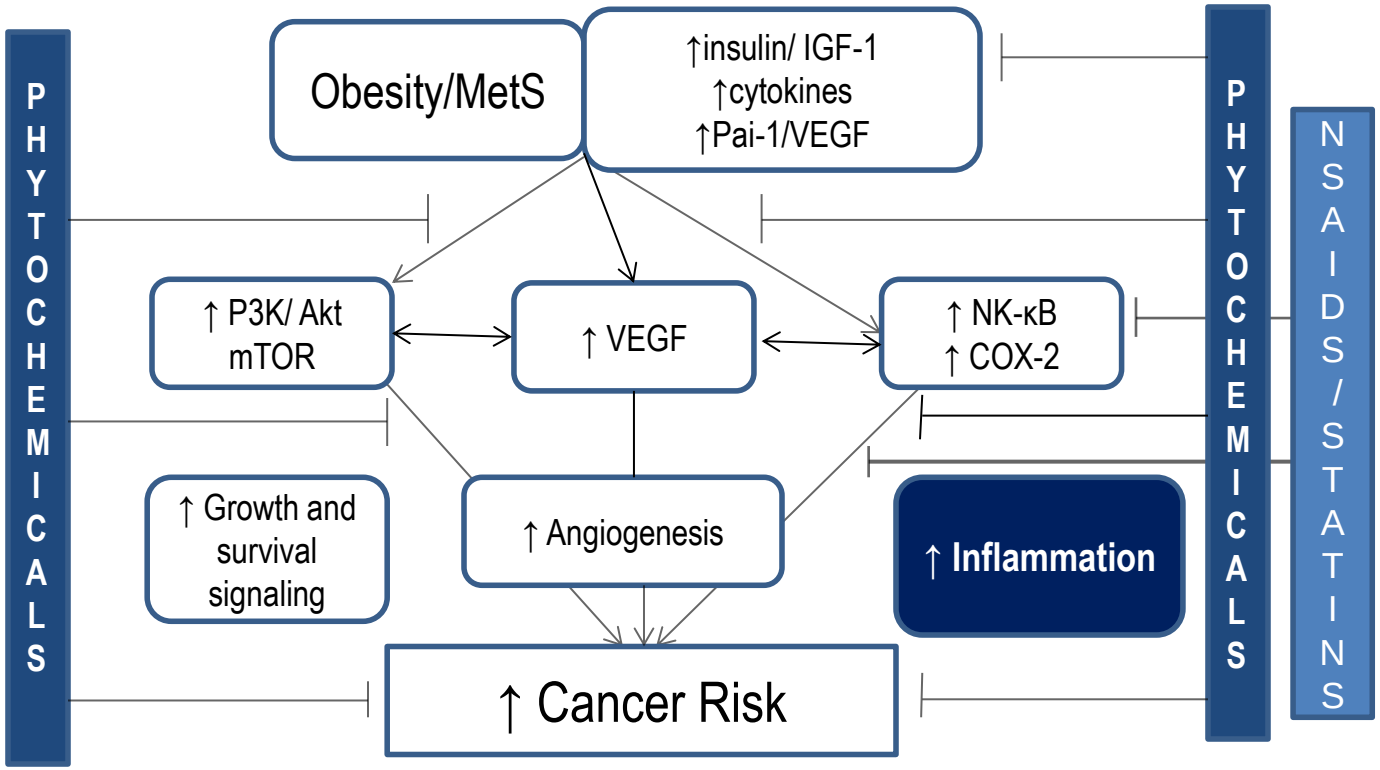
- Inflammation within the host systemically is associated with greater risk for many cancers
- Inflammation within the tumor may be a necessary response to combat disease progression
- Meta-analysis: 30 studies, 2988 patients with CRC
- Results:
  - Tumor-specific inflammation assoc with 41% higher overall and 60% cancer-specific survival
  - High CD8+ cells within stroma; high CVD3+ in invasive tumor margins assoc with improved survival

Mei Z, Liu Y, Liu C, et. Al. B J Cancer, 2014

Interplay with the Gut Microbiome



COLORECTAL CANCER



Inter-related Mechanistic Targets for Dietary Components and Pharmaceuticals

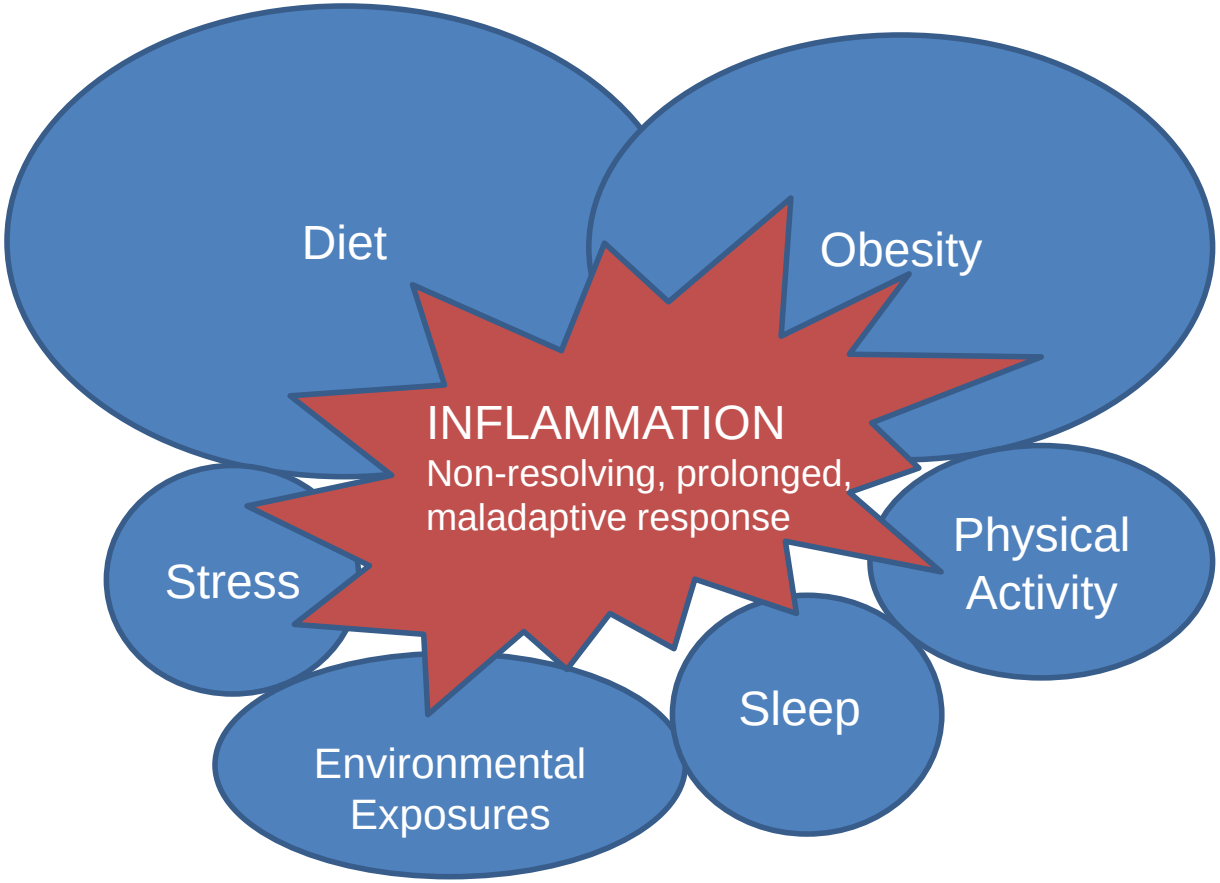
Adapted from Ford NA et al. Frontiers in Oncology, 2013

Summary

- Inflammation is a hallmark of cancer
- Strong evidence exists to support a role for inflammation in cancer development and progression
- Pathogens and related or unrelated inflammation may further exacerbate risk
- Targeted approaches to reduce inflammation hold promise to reduce cancer risk

OBESITY, CANCER & INFLAMMATION

Interplay of Diet-Obesity-Inflammation and Cancer



WHAT YOU NEED TO KNOW ABOUT OBESITY AND CANCER

American Institute for Cancer Research

UPDATED: MARCH 2015

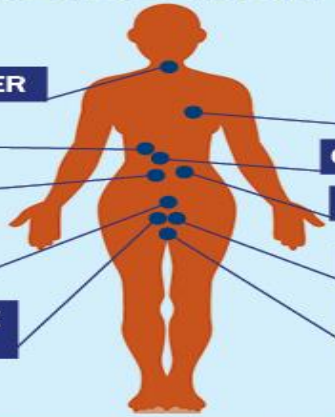
After not smoking,

BEING AT A HEALTHY WEIGHT

Is THE MOST IMPORTANT THING you can do to prevent cancer.

Overweight and obesity

INCREASE RISK FOR[1]



- ESOPHAGEAL CANCER
- LIVER CANCER
- KIDNEY CANCER
- COLORECTAL CANCER
- ADVANCED PROSTATE CANCER
- POST-MENOPAUSAL BREAST CANCER
- GALLBLADDER CANCER
- PANCREATIC CANCER
- OVARIAN CANCER
- ENDOMETRIAL CANCER

AICR ESTIMATES THAT EXCESS BODY FAT IS A CAUSE OF APPROXIMATELY

121,700

U.S. CANCER CASES EVERY YEAR.[2]

AND YET...

7 in 10 Americans are currently overweight or obese.[3]

AND ...

Only about half of all Americans are even aware of the obesity-cancer link.[4]

PROTECT YOURSELF!

Move More

Eat Smart

For tips on getting to, and staying at, a healthy weight, visit www.aicr.org

1. AICR/WCRF Expert Report (2007) and Continuous Update Reports (Ongoing). 2. AICR/WCRF Policy Report (2009) and 2015 preventability update.
3. US Center for Disease Control and Prevention: Obesity and Overweight. 4. 2015 AICR Cancer Risk Awareness Survey

The evidence is the latest from the *Continuous Update Project* (CUP), which systematically updates and reviews the research conducted worldwide into cancer risk related to diet, physical activity and body weight. All the evidence gathered is then assessed by a panel of independent scientists who make recommendations for cancer prevention.

CUP Continuous Update Project

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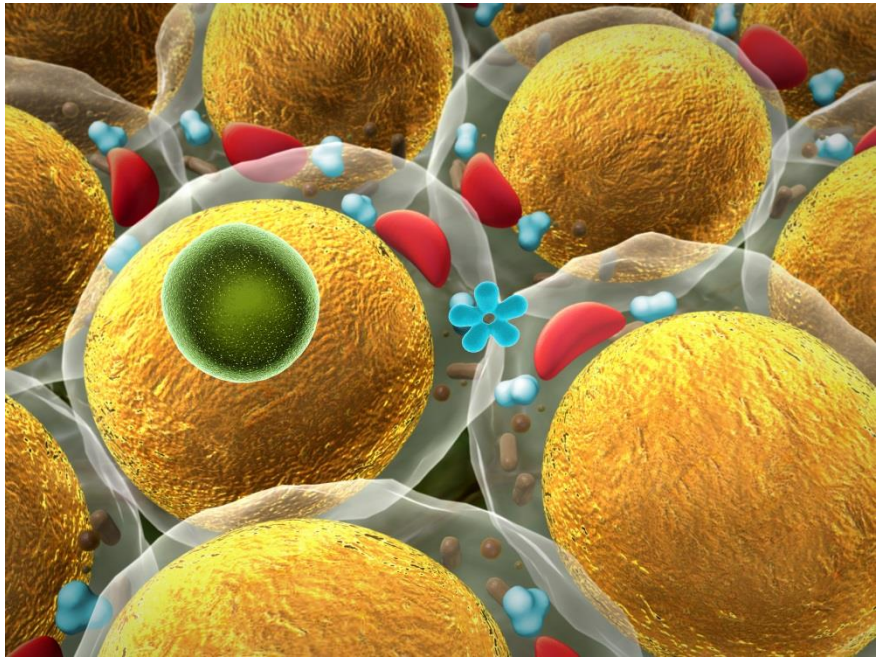
Adipocyte and Inflammation



CD4+ regulatory T cell
CD8+ effector T cell
M2 macrophage
M1 macrophage
Vessels
Dead adipocyte

Adipocyte stromal cells have high concentrations of immune cells and angiogenic potential and as such may contribute to cancer progression

Lee et al. Curr Opin Clin Nutr Metab Care, 2010.

Obesity-associated Chemoresistance: Primary Role of Inflammation

- Metabolic perturbations
- Impaired drug delivery
- Chronic low-grade inflammation
- Adipose tissue expansion
- Altered pharmacokinetics
- Increased tumor-associated microphages

Lashinger LM et al. Clinical Pharmacology & Therapeutics, 96:459-463, 2014.

BIOMARKERS

Inflammation-associated Biomarkers and Cancer

Biomarker	Role
Insulin	Growth-promotion/ cell division, anti-apoptotic
IGF-1 and IGF-BP-1	Increased cell migration, prolonged elevated insulin, potentiates growth factors
C-reactive protein (CRP)	Inflammation, may correlate with estradiol
Interleukin 6	Inflammation, growth and differentiation of malignant cells
Tumor necrosis factor alpha	Inflammation, associated with insulin resistance
Serum amyloid A (SAA)	Low-grade, chronic inflammation
NF-kB signaling	Transcription factor family associated with immunity and inflammation

Cytokines and Cancer Prognosis: Examples

- IL-6 – elevated in tumor, serum and peritoneal fluid of ovarian cancer patients (Coward and Kulbe, 2012)
- C-Reactive protein/ albumin ratio predicts survival in hepatocellular cancer (Kinoshita et al, 2015)
- IL-6 associated with lung cancer mortality in Blacks and NHW; Il-10 associated with increased survival in Blacks (Enewold et al, *CEBP*, 2009)
- Macrophage infiltration has been associated with angiogenesis and prognosis in women presenting with breast cancer (Leek RD et al, *Cancer Res*, 1996)

Inflammation and Cancer Prognostic Scores: The Glasgow Prognostic Index

Systemic inflammation-based prognostic scores	Score
C-reactive protein ≤ 10 mg/l and albumin ≥ 35 g/l	0
C-reactive protein ≤ 10 mg/l and albumin < 35 g/l	0
C-reactive protein > 10 mg/l and albumin ≥ 35 g/l	1
C-reactive protein > 10 mg/l and albumin < 35 g/l	2
Neutrophil count:lymphocyte count < 5:1	0
Neutrophil count:lymphocyte count ≥ 5:1	1
Platelet count:lymphocyte count < 150:1	0
Platelet count:lymphocyte count 150-300:1	1
Platelet count:lymphocyte count ≥ 300:1	2
C-reactive protein ≤ 10 mg/l and white cell count ≤ 11 x 10^9/1	0
C-reactive protein ≤ 10 mg/l and white cell count > 11 x 10^9/1	1
C-reactive protein > 10 mg/l and white cell count ≤ 11 x 10^9/1	1
C-reactive protein > 10 mg/l and white cell count > 11 x 10^9/1	2
Albumin (g/l) + 5 x total lymphocyte count x 10^9/l ≥ 45	0
Albumin (g/l) + 5 x total lymphocyte count x 10^9/l ≥ 45	1

GPS associated with:

- Undesirable weight loss
- Loss of muscle mass
- Higher comorbidity
- Increased pro-inflammatory cytokines
- Increased angiogenesis
- High prognostic value in cancer

Proctor MJ et al. Eur J Cancer, 47: 2633-2641, 2011; Martin HL. Intl J Med, 2014;
McMillan DC. Ca Treatment Rev, 2013; McMillan DC. Curr Opin Clin Nutr Metab Care, 2009.

The GPS: CRP, Albumin and the Ratio:

Pretreatment Measures Predict Survival in Hepatocellular Cancer

- 186 hepatocellular carcinoma patients
- Evaluated CRP/albumin ratio at the time of diagnosis
- Ratio above 0.037 was associated with progressive disease
- Performed better/ predicted survival more accurately than Glasgow prognostic score, and neutrophil lymphocyte ratio
- More recent report suggest CRP independently predicts prognosis in HCC patients

Kinoshita A et al. Ann Surg Oncol, 2014

Inflammation, Diet and Survival

- CRP and inflammation overall is associated with poorer survival (Al Murri et al, 2006(breast); Jamieson et al, 2005(pancreas); Lamb, 2006 (renal clear cell); Crozier et al, 2006(CRC)).
- Inflammation is pathogenic in cancer-associated malnutrition (Argiles et al, 2003).
- Malnutrition is associated with higher mortality in patients with cancer (AND Evidence Analysis Library).
- Malnutrition, including hypoalbuminemia, in patients with cancer is commonly responsive to MNT.

Summary

- Several cytokines have been implicated in relation to cancer risk and prognosis
- Obese individuals commonly present with chronic, low-grade inflammation expressing many of the cytokines also associated with cancer risk
- The *combination* of obesity and infection may further exacerbate risk for select cancers
- Dietary modification, including weight management and/or MNT targeting low albumin, may attenuate inflammatory response and in turn modify cancer risk and/or survival

DIET-DERIVED INFLAMMATION

Fatty Acids

Omega 6			Omega 3		
Corn-fed animal products, oil-based salad dressings			Fish, walnuts, seeds, dark leafy greens, grass-fed animal products		
Effecting enzymes of metabolism:					
Cyclooxgenase (COX)		Lipoxygenase (LOX)		Cytochrome P450 (CYP)	
Which in turn induce the activity of:					
Thromboxanes	Prostacyclins	Prostaglandins	Lipoxins	Leukotrienes	Epoxyeicosatrienoic acid

Adapted from Arnold, et al. Pharmacological Reports, 2010. *Human Metabolome Database.*

Sodium and Inflammation

- Sodium intake remains high in US adults
- High sodium/salt intake has been associated with inflammation
- Limited study of sodium intake and cancer

Zhang WC et al., Cell Res, 2015

Advanced Glycation End-products & Inflammation

- AGE abundant in diet: N-Carboxymethyllysine (CML)
  - Proteins
  - Saturated fats
  - Red meat, white meats, processed meats
  - High temperature cooking
- Mechanistically associated with oxidative stress (lipid peroxidation), insulin resistance and inflammation
- AGE intake has been associated with pancreatic cancer in men (AARP study)
- Study of 24 adults randomized to high vs low AGE diet for 6 weeks showed no change in exposure or inflammation (IL-6, CRP, TNFαR)

Van Puyvelde K, Mets T, Njemini R, Beyer I, Bautmans I. Nutr Rev. 2014;
Jiao, et al, Am J Clin Nutr, 2015; Semba RD et al,J Nutr. 2014

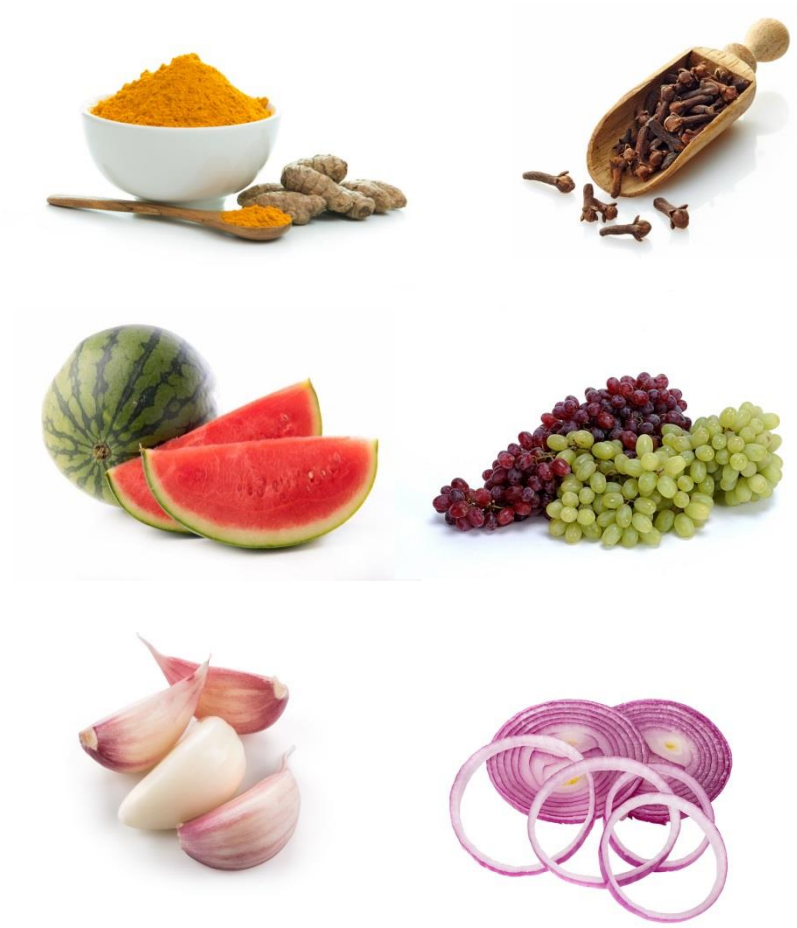
Dietary Patterns and Inflammatory Biomarkers

- Systematic Review: Barbaresko et al, ILSI, 2013
- 46 studies, representing 70,659 study participants
- 95% diet data estimated by Food Frequency Questionnaire
- Most common food choices were associated with elevated CRP
- Eating patterns associated with inflammation included: beer, red and processed meats.
- Il-6 associated with sweet and dessert pattern as well as high-fat dairy and red meat, alcohol patterns

DIET-DERIVED ANTI-INFLAMMATORY EFFECTS

Anti-inflammatory Modulating Dietary Components

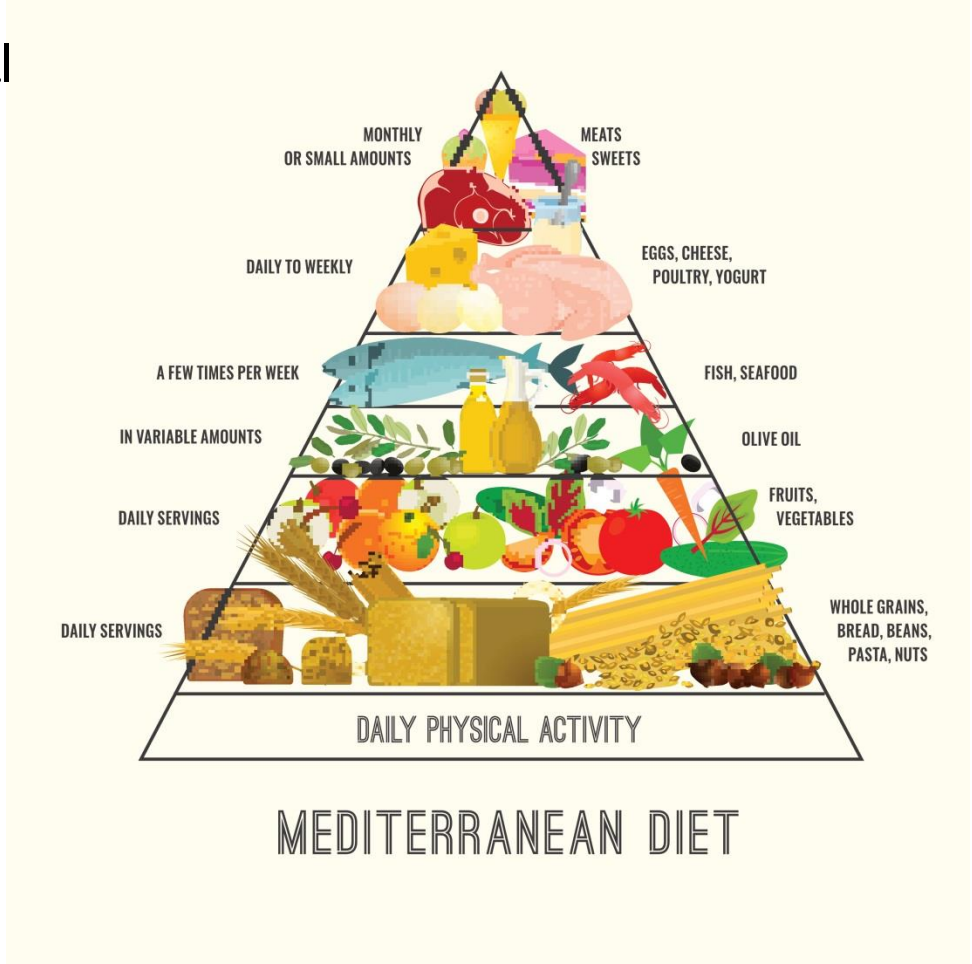
- Allicin -onions
- Catechins- green tea
- Cinnamaldehyde - cinnamon
- Curcumin – tumeric
- Lycopene –tomato products, watermelon
- Omega-3 fatty acids
- Polyphenols- tea, berries
- Reservatrol – grapes
- Sulforaphane and di-indolylmethane – broccoli/cruciferae



Kannappan R et al. Mol Neurobiol, 2001.
Cardozo L et al. Biochimie, 2013.

Anti-inflammatory, Mediterranean Diet

- Observational and interventional evidence for anti-inflammatory effects of MED pattern
- Some epidemiological evidence to support lower cancer risk
- RCT lacking in terms of cancer survival



Barbaresko J et al, ILSI, Nutrition Reviews, 2013. Food pyramid Courtesy of Oldways, oldwayspt.org.

MED Diet and Inflammation

Author	Sample, Country	Duration	Change in Biomarker
Bluher	109, Israel	2 y	↓ CRP and MCP-1
Konstantinidou	60, Spain	3 mo	↓ CRP, ↓P-selectin, ↔ MCP-1
Esposito	90, Italy	Cross-sectional	↓ CRP, IL-6, IL-18
Azzini	131, Italy	Cross-sectional	↑ IL-10,↓TNFα
Carter	13,197, USA	Cross-sectional	↓ CRP, ↓fibrinogen
Dedoussis	957, France, Greece, Italy, Poland, Germany	Cross-sectional	↓ IL-8, ↔ MCP-1, CRP and TNFα
Panagiotakos	3042, Greece	Cross-sectional	↓CRP and fibrinogen
Fung	660 women, USA	Cross-sectional	↓CRP, IL-6, E-selectin, VCAM-1; ↔ ICAM-1

Barbaresko J et al. Nutr Rev, 2013

Dietary Inflammatory Index

- A composite score was needed to estimate overall inflammatory effect of a multi-component diet that includes pro and anti-inflammatory foods.
- 6500 peer-reviewed manuscripts were reviewed that evaluated one or more dietary components and one or more inflammatory indices
- International with standardization to global referent values in assigning inflammatory / anti-inflammatory potential
  - Maximum pro-inflammatory diet score: +7.98
  - Maximum anti-inflammatory score: - 8.87
- Associated with hs CRP (Shivappa et al, PHN, 2013)

Sample Foods and Inflammatory Score

Foods / Dietary Component	Overall Inflammatory Effect Score
Alcohol	-0.278
B-carotene	-0.584
Fiber	-0.663
Garlic	-0.412
Isoflavones	-0.593
N-3 fatty acids	-0.436
Onion	-0.310
Tea	-0.536
Tumeric	-0.785
Vitamin C	-0.424
Vitamin D	-0.446
Energy	+0.180
Fat	+0.298
Saturated fat	+0.373

Adapted from Shivappa et al, PHN, 2013

Construct Validation

Association between quintiles of the FFQ-derived DII and biomarkers of inflammation

SEASONS study	Asklepios Study
• Higher DII score associated with > risk for hsCRP above 3mg/dl • $OR_{adjusted}$ 1.10 (1.02-1.19) using 7 day diet records	• Higher DII score associated with > risk for IL-6 above 1.6 pg/ml • $OR_{adjusted}$ 1.19 (1.04-1.36)

- Head and neck cancer patients (n=160): whole foods diet associated with lower IL-6, TNFα and IFN-γ)

Models adjusted for age, body mass index, race/ethnicity, educational level, smoking status, physical activity, use of NSAIDs, statins, inflammation-related co-morbidities (history of inflammatory disease, cancer stage)

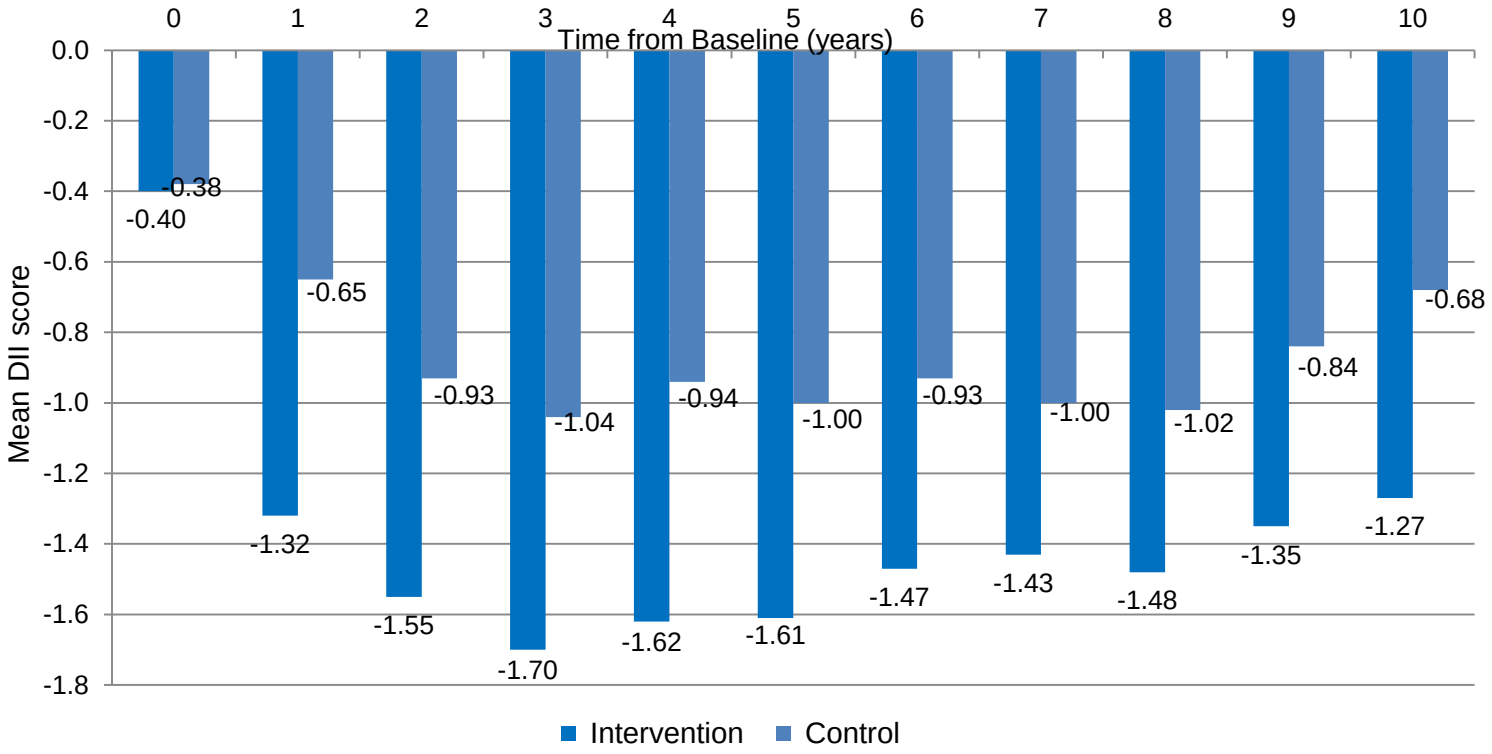
Shivappa, PHN, 2013; Shivappa, Br J Nut, 2015; Arhtur et al, Cancer, 2014

Distribution of Food Groups in Quintiles (Q) of the DII: WHI CT&OS

Food group (medium servings/day)	Q1 (-7.055, <-3.136) (healthiest)	Q2 (-3.136, <-1.995)	Q3 (-1.995, <-0.300)	Q4 (-0.300, <1.953)	Q5 (1.953, 5.636) (least healthy)
Fruits	2.71	2.04	1.85	1.73	1.73
Vegetables	3.15	2.30	2.12	2.00	2.00
Combo Fruit/Veg	5.86	4.34	3.97	3.73	3.73
Fish	0.07	0.07	0.07	0.07	0.07
Red meat	0.63	0.73	0.74	0.76	0.76
Poultry	0.44	0.40	0.38	0.38	0.38
Soy	0.08	0.02	0.02	0.02	0.02
Nuts	0.26	0.20	0.18	0.17	0.17
Combo Nut/soy	0.34	0.22	0.20	0.18	0.18
Grains	5.89	4.69	4.55	4.47	4.47
Whole Grain	1.73	1.24	1.17	1.12	1.12
Milk	0.97	0.88	0.80	0.71	0.71
Dairy	2.30	2.06	1.92	1.76	1.76

Courtesy of Susan Steck, USC Cancer Center

Mean DII Scores Across Years of Follow-up in the DMT



P-value for the difference in DII scores between intervention and control was 0.62 at baseline, and <0.0001 for each year from year 1 onwards

Courtesy of Susan Steck, USC Cancer Center

Breast Cancer Incidence and Mortality Across Dll Tertiles

	T1 (-7.05, <-2.37) (healthiest)	T2 (-2.37, <0.47)	T3 (0.47, 5.79) (least healthy)	P_{trend}
Breast cancer cases, n=1922	2155	1912	1774	
Breast cancer, HR (95%CI)[a]	1.00 (ref)	0.95 (0.89, 1.01)	0.99 (0.92, 1.06)	0.89
HER2+ cases, n=662	215	222	225	
HER2+ cancer, HR (95%CI)[a]	1.00 (ref)	1.12 (0.92, 1.35)	**1.29 (1.05, 1.59)**	0.01
Breast cancer mortality,	117	136	153	
Breast cancer mortality, HR (95%CI) [b]	1.00 (ref)	1.06 (0.81, 1.37)	**1.30 (0.99, 1.71)**	0.04

[a]adjusted for age, race/ethnicity, body mass index, physical activity, education, smoking status, mammography within 2 years of baseline, age at menarche, number of live births, oophorectomy status, hormone therapy use, NSAID use, dietary modification trial arm, hormone therapy trial arm, calcium and vitamin D trial arm, and total energy intake; [b]adjusted for age, race/ethnicity, body mass index, physical activity, education, smoking status, mammography within 2 years of baseline, hormone therapy use, NSAID use, dietary modification trial arm, hormone therapy trial arm, calcium and vitamin D trial arm, total energy intake, estrogen receptor status, progesterone receptor status, stage and time since diagnosis

Patterns of Change in DII and Breast Cancer Risk

	Patterns of DII quintile changes				
	Anti-inflammatory stable	**Anti-inflammatory change**	**Neutral inflammation stable**	**Pro-inflammatory change**	**Pro-inflammatory stable**
Invasive breast cancer	1.00 (ref)	0.91 (0.81, 1.02)	0.91 (0.83, 0.99)	0.98 (0.88, 1.10)	0.94 (0.85, 1.04)
Triple negative (ER−, PR−, HER2−)	1.00 (ref)	**0.47 (0.28, 0.79)**	0.88 (0.63, 1.22)	1.02 (0.68, 1.52)	0.93 (0.66, 1.33)
ER−, PR−, HER2+ subtype	1.00 (ref)	1.14 (0.57, 2.28)	1.38 (0.79, 2.39)	1.46 (0.79, 2.82)	1.60 (0.91, 2.80)
Luminal A (ER+ and/or PR+, HER2−)	1.00 (ref)	0.94 (0.81, 1.10)	0.92 (0.81, 1.04)	1.03 (0.89, 1.19)	0.88 (0.77, 1.01)
Luminal B (ER+ and/or PR+, HER2+)	1.00 (ref)	0.92 (0.62, 1.35)	0.84 (0.61, 1.15)	0.92 (0.61, 1.37)	1.11 (0.80, 1.54)

All models were adjusted for age, race/ethnicity, education, smoking status, physical activity, body mass index, NSAID use, category and duration of estrogen use, category and duration of estrogen & progesterone use, and total energy intake.

Courtesy of Susan Steck, USC Cancer Center

DII and Cancer Risk Associations

- WHI prospective study of colorectal cancer risk
- Iowa Women's Health Study and CRC risk
  - Colon: $HR_{age\text{-}adj\ Continuous}$: 1.08 (1.02-1.13);$_{Categorical}$1.28 (1.08-1.53)
  - Rectal: HRage-adj 1.13 (0.98-1.31)
- Higher risk in the Bellvitge case-control analysis
  - Colorectal: OR 1.66 (1.08-2.56); Colon: OR 2.24 (1.33-3.77)
- Italian case-control studies of pancreatic cancer and separately prostate cancer risk also show elevated risk of 24% and 33%, respectively

Shivappa et al, Br J Nutr, 2014; Shivappa et al, CEBP, 2014; Zamora-Ros et al, 2015; Shivappa et al, Br J Nutr, 2015

DII and Length of Stay: CRC Surgery

- 689 patients undergoing surgical resection of colon for cancer in Krakow, Poland
- FFQ by interview prior to surgery, on admission to hospital
- Mean hospitalization: 10.9 (9.4) days
- Overall linear regression showed inverse association (b=0.59)
- The effect was driven by patients under age 60 y
- Higher DII score is associated with 39% reduction in mortality in patients with distant metastatic disease

Galas, Kulig and Kulig, EJCN, 2014; Galas and Kulig, J Cancer Res Clin Oncol, 2014

EVIDENCE

Role of Weight Loss in Reducing Inflammation

Evidence in Support of Long-term, Moderate Caloric Restriction

- 218 healthy, overweight, non-obese adults
- 25% caloric restriction; 10.4% weight loss over 24 months
- Significant decline in CRP, ICAM-1 and TNF-α with caloric restriction
- WBC and total lymphocytes also lowered during intervention as compared to ad lib diet
- Cell-mediated immunity was not compromised (delayed hypersensitivity antibody response testing)

Meydani SN et.al., Aging, July, 2016

Nutrition, Exercise and Women Study

- Ancillary study designed to test effect of modest weight loss on inflammatory markers
- 503 (439 completers) overweight/obese, post-menopausal women
- Diet, exercise or combination x 12 months
- 5% weight loss was associated with significant reductions in CRP, IL-6 and SAA with diet or diet + exercise
- Similarly a trial by Nicklas et al associated w 5.7% loss in BW with reduced inflammatory cytokine levels (AJCN, 2004)
- Reviews suggest consistent reduction in inflammatory markers with weight loss interventions

Imayama I et al. Cancer Research, 2012; Nicklas, AJCN, 2004; Nicklas, CMAJ, 2005

Weight Loss and Inflammatory Response in Breast Cancer Survivors

- 50 overweight breast cancer survivors on Tamoxifen® or aromatase inhibitors
- Randomized, 2-arm trial (Low fat or Low carbohydrate)
- Face-to-face counseling with a dietitian weekly x 4 weeks, then monthly for 5 months
- Baseline, 3 and 6 month measures of:
  - Anthropometrics, body composition
  - Metabolic indices
  - Inflammation (CRP)

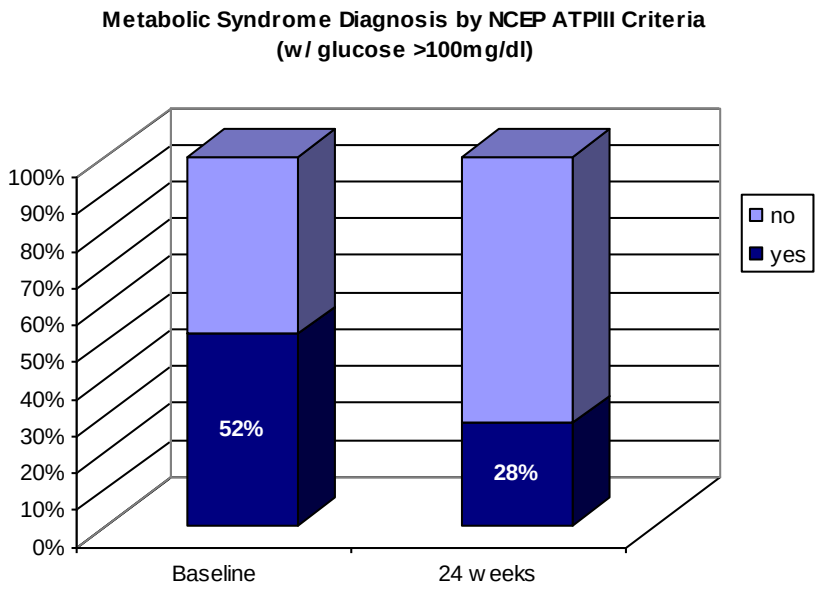
Thomson, et al. Nutr & Cancer, 2010 (Funded by Atkins Research Foundation)

Results

Changes in Inflammatory/ Metabolic Indices

- Mean weight loss 6.1 kg @ 6 months
- Significant reduction in insulin, s. cholesterol/LDL cholesterol, TGL (low CHO)
- hsCRP reduced by -0.4 (p =0.06)
- Study of 68 overweight breast cancer survivors showed reductions in IL-6 and TNF-α after a 16 week diet + exercise weight loss intervention (*Pakiz, 2011*)
- Study of 28 women w/ triple-negative disease (n=13 completers provided diet+exercise). No significant change in inflammatory cytokines (CRP, IL-6, TNFα) (*Swisher, 2015*).

Metabolic Syndrome



Healthy Weight Management Study

- 85 breast cancer survivors; 15 kg > IBW
- Healthy eating, exercise and behavioral modification/CBT
- 16 weekly group sessions, 8 monthly follow-up sessions
- Mean weight loss at 12 months: 5.7 kg (vs 0.2 kg in control)
- At 16 weeks significant reductions in:
  - TNFα in both groups
  - IL-6 in intervention (p=0.06)
  - No change in VEGF or IL-8

On-going Trials in Cancer Survivors

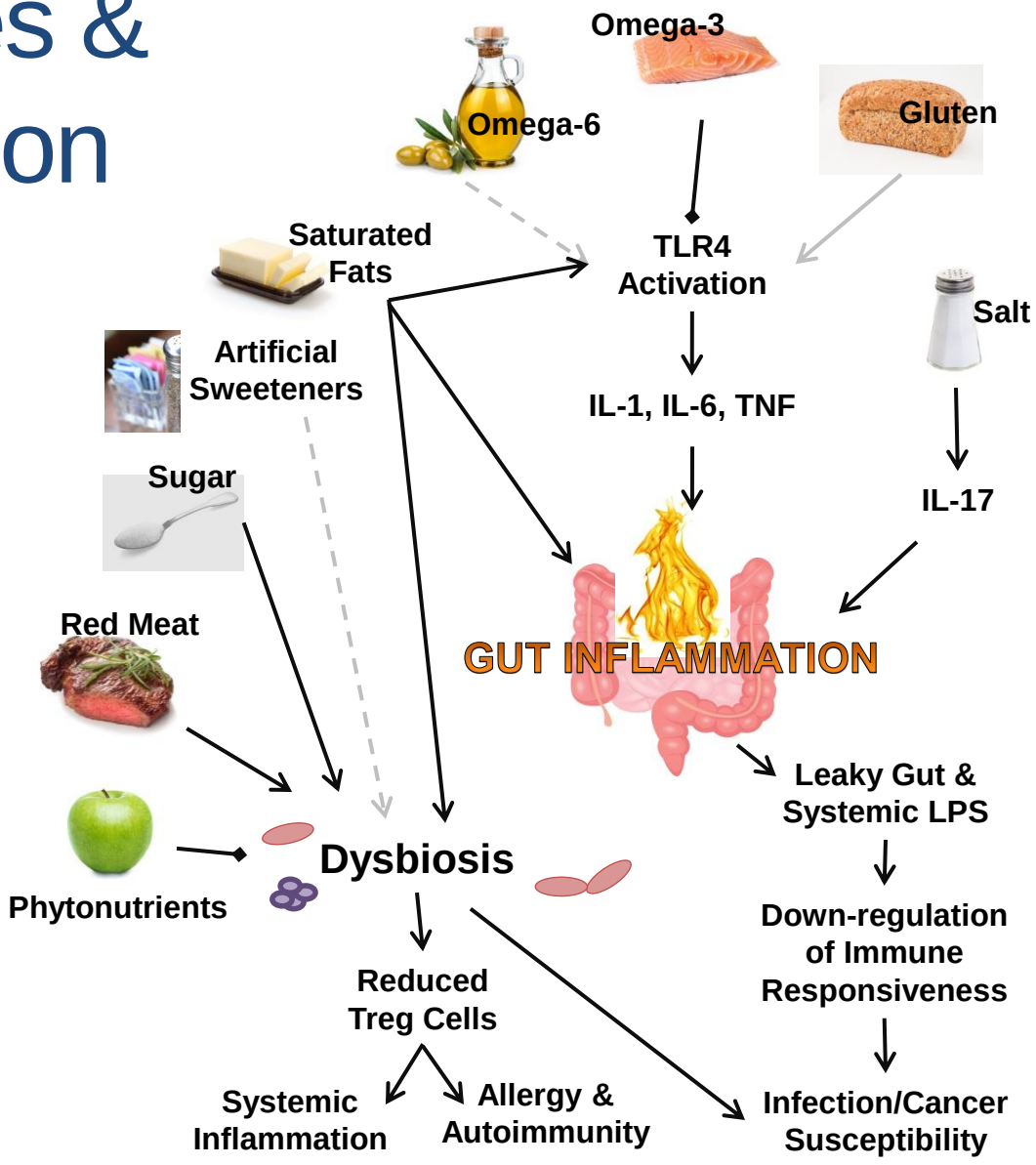
- A large body of evidence supports the therapeutic benefit/ anti-inflammatory effects of modest weight loss in overweight individuals with or without cancer
- Few published with inflammation as primary endpoint; none to specifically modify CRP/albumin ratio
- Pending trials:
  - Low Carbohydrate vs Low Fat (CHOICE) study in breast cancer (Sedlacek, USA)
  - Muscle mass, Omega-3, Diet, Exercise and Lifestyle (MODEL) study in breast cancer survivors (McDonald, Australia)
  - Lifestyle Intervention for ovarian cancer Enhanced Survival (LIVES) study (Thomson and Alberts, USA)
  - Breast cancer Weight, Energy and Lifestyle (BWEL) study: > 3000 early stage obese survivors randomized to modified DPPT / Look AHEAD weight loss program (Ligibel, USA and Canada)

EVIDENCE

Non-weight Loss Diet Interventions to Modulate Inflammation in Cancer

Dietary Choices & Gut Inflammation

Myles IA, Nutrition Journal, 2014



Lignans and Inflammation

Associated with Inflammation:

- NHANES sample
- Flax seed- major dietary source
  - Enterodiol
  - Enterolactone
- Every 1% increase in urinary lignans was associated with a 8.1% decrease in CRP and 1.9% decrease in WBC count
- Lignans have also been associated with lower cancer risk

Eichholzer M, Ca Causes Control, 2014

Tetrahydrocurcumin

Tumeric

THC

- Increased bioavailability over curcumin
  - Self-microemulsifying drug delivery system (research compounds)
- Regulation of oxidative stress
- Anti-inflammatory
- Neuroprotective

Wu J-C et al, Royal Society of Chem, 2014

Olive Oil

Virgin / Extra Virgin

Review of Evidence

- Polyphenols
- Inhibition of:
  - COX-2
  - iNOS
  - Macrophage inflammatory protein (MIP-1)
  - PGE2 synthase
  - IL-6 mRNA expression
  - Nrf2 – BARD- synthetic oleanane triperpenoid

Cardeno A, Sanchez-Hidalgo M, Alarcon-de-la-Lastra C, Curr Medicinal Chem, 2013

Nrf2: Master Switch

- Resveratrol
- Curcumin
- Sulfurophane
- Allicin
- Lycopene
- Cinnamaldehyde
- Vitamin E
- Coffee
- Cocoa

Cardozo et al, Biochime, 2013;
Martin, Goya and Ramos, Food and Chem Tox, 2013

Increased Fruit and Vegetable Intake

- SAA, IL-6 and/or CRP are biomarkers of poor prognosis in cancer
- Use of biosamples from two fruit and vegetable intervention trials, one in patients with hypertension (n=112) and one in aging patients (n=82)
- Intervention of 6 svg/8weeks and 5 svg/16 weeks, respectively
- hsCRP, IL-6 were not changed
- SAA was inversely associated with increase in fruit and vegetable intake

Nadeem et al, Br J Nutr, 2014, 112, 1129-36

NHANES0 Eating Frequency and Breast Cancer Risk

- NHANES 2009-10; 2650 adult women;
- Exposure: single 24-hour recall; eating timing and frequency
- Outcome: hsCRP
- Evening calories < 30% total combined with prolonged overnight fast was assoc. with an 8% lower breast cancer risk
- Each 10% increase in evening calories consumed associated with a 3% higher CRP
- Eating 1 additional meal/day assoc. with 8% lower CRP

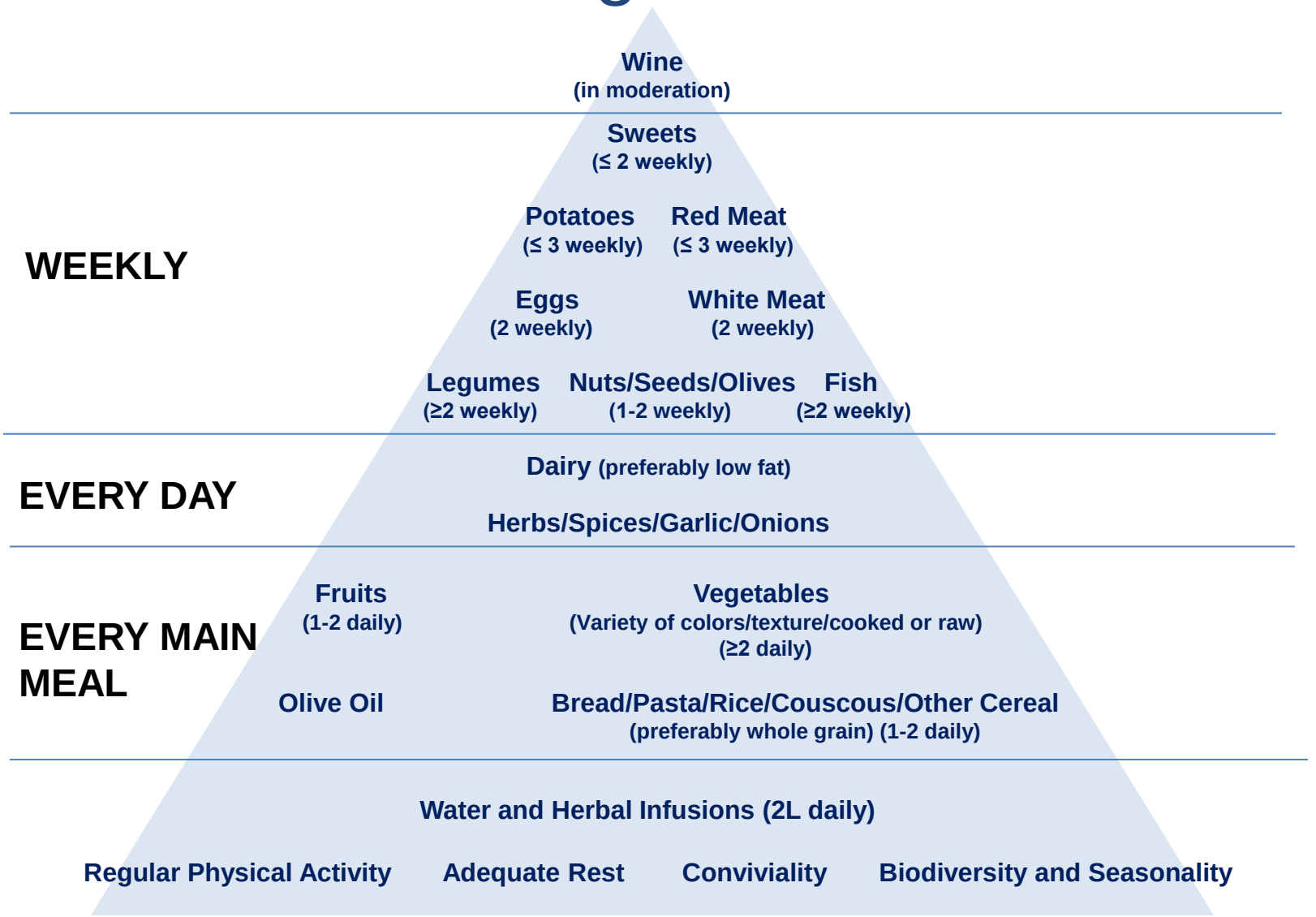
Marinac CR et. al., PLOS One, 2015

PRACTICE APPLICATIONS

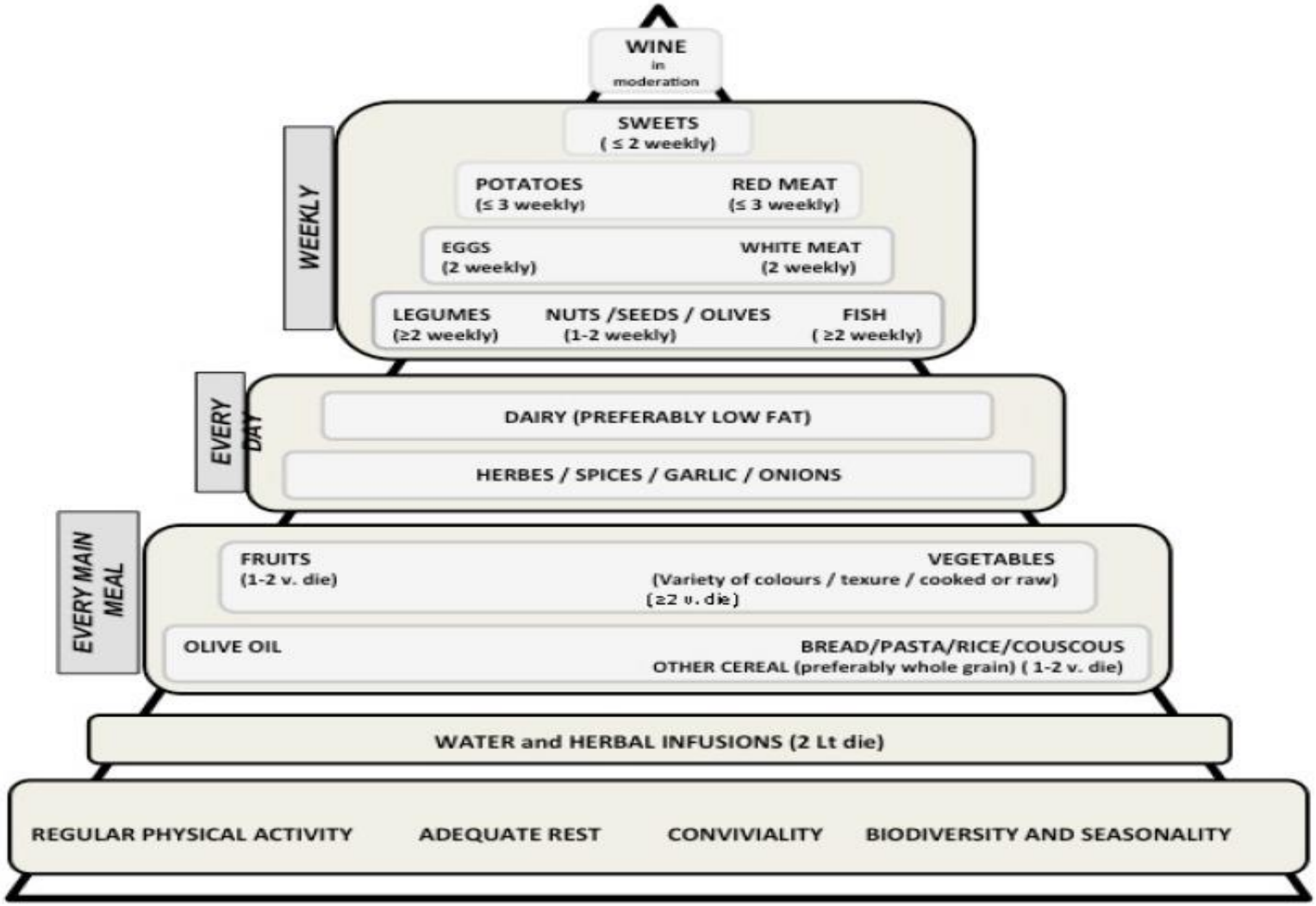
What Are The Options For Medical Nutrition Therapy?

- **Modify diet to reduce inflammation**
  - Quality diet: nutrients and bioactive compounds
  - Anti-inflammatory diet, DII, Mediterranean diet
  - Meal patterning: eating frequency, intermittent fasting
- **Weight control**
- **Multidisciplinary efforts**
  - Combination therapies: Anti-inflammatory medications and diet
    - Reduce inflammation, reduce toxicity and enhance diet quality to reduce cancer/recurrence risk
  - Other lifestyle factors
    - Sleep, stress management, physical activity

Mediterranean Anti-inflammatory Eating Pattern



Mediterranean Anti-inflammatory Eating Pattern



Plant-based Diets to Modulate DII

- RCT: vegan (n = 12), vegetarian (n = 13), pescovegetarian (n = 13), semivegetarian (n = 13), or omnivorous (n = 12).
- 24 hour recall at 2,6 months
- All non-omnivore diets were associated with a significant reduction in DII score by 2 months
- Whether this translates to lower inflammatory status is yet to be determine

Turner-McGrievy GM, Wirth MD, **Shivappa** N, Wingard EE, Fayad R, Wilcox S, Frongillo EA, Hébert JR. Nutr Res. 2015

Reduce Advanced Glycation End-products

- Evidence limited and remains controversial
- Reducing AGE in diet is possible
- Plant-based vs meat avoidance
  - Lower fat, saturated fat
  - Fresh foods
- Instruction to reduce high-temperature and dry cooking methods
  - Less frying, roasting, baking, grilling
  - “Charred” food products

Weight Management

- Avoid even small, incremental increases in weight
- Alert to visceral adiposity
- Diet (energy restricted) + physical activity (cardio, weight-bearing and resistance)
- Self-monitoring
  - Diet
  - Weight
  - Activity
  - Body fat /waist circumference

Meal Timing and Fasting

- Feeding associated with post-prandial inflammatory response
  - > Meal frequency may reduce CRP, but reducing evening energy consumption is also necessary
  - May be attenuated by addition of anti-inflammatory foods to meal
- Ramadan fasting (n=50)
  - Fasting associated with significant reductions in IL-1β, IL-6 and TNFα
  - Rebound on re-feeding

Dow et al, J Nutr, 2013; Faris et al, Nutr Res, 2012; Marinac et al, PLOS One, 2016

Where Are We Now?

- Large body of evidence that inflammation contributes to cancer risk
- Compelling evidence that select inflammatory biomarkers have prognostic value for cancer
- Basic science and epidemiological evidence suggest that diet/dietary components can modify the inflammatory response
- Limited, but generally supportive evidence in cancer survivors that inflammatory response can be favorably modified to improve cancer outcomes
- **The potential for RDN to impact health in those at risk for or treated for cancer through dietary guidance promoting anti-inflammatory dietary approaches is significant**

QUESTIONS?

Thank you!

Credit Claiming

You must complete a brief evaluation of the program in order to obtain your certificate. The evaluation will be available for 1 year; you do not have to complete it today.

Credit Claiming Instructions:

1. Go to www.CE.TodaysDietitian.com/HormelInflammation **OR** Log in to www.CE.TodaysDietitian.com and go to My Courses and click on the webinar title.
2. Click Take Course on the webinar description page.
3. Select Start/Review Course to complete and submit the evaluation.
4. Download and print your certificate.

Please Note: If you access the Evaluation between 3:30-4:30 pm ET on 8/31, you may experience a slow connection due to a high volume of users.