MAKING CANCER PERSONAL Selected Bio Markers That Guide the Use of Natural Compounds

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- Independent Contractor and Lecturer Providing Educational Services to Nutraceutical Companies
- Principal and Founder, American Institute of Integrative Oncology Research and Education and Integrative Cancer Answers that derive revenue from educational products and services and sales of supplements

LEARNING OBJECTIVES

- Understand and identify selected prognostic and predictive risk factors and biomarkers that promote a carcinogenic and tumorogenic bioterrain
- Understand how to monitor selected biomarkers utilizing laboratory assays
- Understand and identify biomarker informed interventions utilizing natural compounds and functional foods for managing and reducing cancer risk and promoting normal function
- Understand how to develop a biomarker informed personalized cancer risk reduction care plan to promote a microenvironment that is not supportive of the development, growth or spread of cancer



BONUS : WHAT COMMON BLOOD TESTS REVEAL ABOUT CANCER RISK

DOWNLOAD LINK:

http://aiiore.com/nanp2020

What if Every **Cancer** Patient Had a Plan for their HEALTH and NOT Just a Plan for their DISEASE?



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Selected PROGNOSTIC and PREDICTIVE BIOMARKERS in the TUMOR MICROENVIRONMENT

- Coagulation
- Copper
- Vitamin D
- Inflammation
- Insulin Resistance and Obesity



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RECOGNIZING THE PATTERN OF MALIGNANCY: THE CANCER TERRAIN

Develop a biomarker informed personalized cancer risk reduction care plan to promote a microenvironment inhospitable to the development, growth and spread of tumor cells The tumor microenvironment contributes to every aspect

of carcinogenesis

Current Cancer Drug Targets, 2014, 14, 30-45 Role of Inflammation-Associated Microenvironment in Tumorigenesis and Metastasis Feng Gao, et al

TUMOR MICROENVIRONMENT

The cellular environment in which the tumor exists, including surrounding blood vessels, immune cells, fibroblasts, bone marrow-derived inflammatory cells, lymphocytes, signaling molecules and the extracellular matrix (ECM)

The tumor and the surrounding microenvironment are closely related and interact constantly

The tumor microenvironment contributes to tumor heterogeneity and behavior

Create an Environment Inhospitable to the Development, Growth, Proliferation and Spread of Tumor Cells

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THE HALLMARKS of CANCER

> Cancers 2016, 8(3), 35; **Review** Mechanisms of Nuclear Export in Cancer and Resistance to Chemotherapy Mohamed El-Tanani, et al

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INCREASING DEMAND FOR FRONTLINE CARE PROVIDERS

Are We Meeting the Needs of the Rising Tide of Cancer Patients and Cancer Survivors???



Cancer Survivors & Thrivers These patients are already in our practices

There are close to

14 million cancer survivors

living in the U.S., a number that is expected to grow to

19 million by 2024,

according to the National Cancer Institute.

About 40% have been alive 10 years or more after diagnosis.



¹ DeSantis C, Chunchieh L, Mariotto AB, et al. (2014). Cancer Treatment and Survivorship Statistics, 2014. CA: A Cancer Journal for Clinicians. In press.

Cancer Survival Among US Whites and Minorities

American Cancer Society: Cancer Treatment and Survivorship | Facts and Figures 2014-2015





Oncologists' and Primary Care Physicians' Awareness of Late and Long-Term Effects of Chemotherapy

J. Oncol Pract Mar 1 2014:e29-e36

Primary Care Providers **awareness** of late and long-term effects of chemotherapy **was limited**

Education for all providers caring for a growing population of cancer survivors is needed

Cancer Journey & Cancer Survivorship

- Transforming
 Outcomes & Prognosis
- Enhancing Oncology
 Treatments
- Managing Short Term and Long Term Adverse Effects
- Providing A Health Model











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PRIMARY STRATEGIES for Inhibiting Carcinogenesis: Change the Signaling Environment

PREVENTION | INHIBIT TUMOR INITIATION & PROMOTION block toxic and mutagenic effects to DNA, promote apoptosis and normal cell cycling

BLOCK CANCER PROLIFERATION & PROGRESSION control signal transduction, block angiogenesis & growth factors, modulate endocrine immune functions & inflammation, promote apoptosis

BLOCK INVASION & METASTASIS regulate cell-adhesion molecules, protect extracellular matrix (ECM) from degradation, inhibit up-regulation of genes that block metastasis

SELECTED BIOMARKERS

Monitoring the Tumor Microenvironment

BIOMARKERS | Tumor Microenvironment

- Coagulation Factors Elevated levels of coagulation factors may be an early sign of tumor development and can indicate increased cancer risk.
- Copper Status Increased copper may be an early sign of cancer progression and angiogenesis.
- Inflammation Inflammation increases risk for cancer occurrence and death from cancer.
- Vitamin D Low vitamin D levels may indicate an increased risk for cancer occurrence and progression.
- Insulin Resistance and Obesity Insulin resistance and obesity increase risk for cancer occurrence and worsen prognosis.

BIOMARKERS (measurable indicators)

- Diagnostic
- Prognostic
- Predictive of interventions for which the patient may derive benefit
- Guide treatment decisions
- Assess response and efficacy of treatments or of disease progression or regression





HYPERCOAGULATION CORRELATED WITH DISEASE STAGE AND PROGNOSIS

Fibrinogen ActivityD-DimerPlateletsLeukocytesC-Reactive ProteinBMI



Activated Coagulation is Prognostic

- Identify early signs of malignancy, progression and recurrence
- Understand tumor microenvironment & relationship between host & factors & tumor factors
- Assess aggressiveness and extent of disease

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Positive Biomarkers of Activated Coagulation are Correlated with

- Elevated Tumor Markers
- Larger Tumor Mass
- Increased Tumor Burden
- Advanced Stage of Disease
- Vascular and Stromal Invasion
- Lymph Node Metastasis
- More Aggressive Disease
- Increased Systemic Inflammation
- Disease Progression
- Disease Free Survival
- Overall Survival
- Response to Chemotherapy



Cancer patients overall have a **7 fold higher risk** of venous thrombosis



Patients with **hematologic malignancies** have a **28 fold higher risk** of Venous thrombosis

Patients with **distant metastases** have a **20 fold higher risk** of venous thrombosis

Postgrad Med J 2006;**82**:642-648 doi:10.1136/pgmj. 2006.046987 Venous thromboembolic disease and & and cancer <u>A Fennerty</u>

VTE is the second most common cause of death in patients with cancer,



but can also be the initial presenting complaint in patients with an occult malignancy.

Nat Rev Clin Oncol. 2012 Jul 10;9(8):437-49. doi: 10.1038/nrclinonc.2012.106. Thrombosis and cancer. Young A et al

Curr Oncol. 2015 Feb; 22(1): 49–59. PMCID: PMC4324343 Clinical challenges in patients with cancer-associated thrombosis: Canadian expert consensus recommendations <u>M. Carrier</u>, et al







Importance of Monitoring and Managing Hypercoagulation and Thrombosis in the Tumor Microenvironment

- Impact on Morbidity, Mortality & Survival
- Individualization of Care
- Early Intervention and Prevention
- Prognostic Value
- Quality of Life



Biomarkers | Pro-Thrombotic Micro Environment

- Leukocytes > 11.0 m/uL inflammation- amplify thrombin generation and platelet adhesion
- Platelets > 350K mm/L inflammation, IL6
- Hemoglobin < 10.0 g/dl inflammation IL1, IL6, TNFa accelerated platelet aggregation
- Fibrinogen activity > 275 mg/dL inflammation
- **D-Dimer**(no consensus) > 250 ng/ml, > 0.30-0.50 DDU
- ongoing fibrinolysis, tumor progression, angiogenesis, metastasis
- BMI <u>></u>35 kg/m²
- (hs-C Reactive Protein > 2.0 inflammation IL6, IL8, TNFa, NFkB not considered an "independent" risk factor")
- Specialty Labs:
 - Tissue Factor P-Selectin

Cancer-Associated Thrombosis: An Overview Clinical Medicine Insights: Oncology 2014:8 Breast. 2015 Oct;24(5):667-72. doi: 10.1016/j.breast.2015.08.003. Epub 2015 Sep 4.

An elevated preoperative plasma fibrinogen level is associated with poor disease-specific and overall survival in breast cancer patients. <u>Krenn-Pilko S¹</u>, <u>Langsenlehner U²</u>, <u>Stojakovic T³</u>, <u>Pichler M⁴</u>, <u>Gerger A⁴</u>, <u>Kapp KS¹</u>, <u>Langsenlehner T⁵</u>.

<u>Cancer Biomark.</u> 2015;15(4):405-11. doi: 10.3233/CBM-150477. **D-dimer and international normalized ratio (INR) are correlated with tumor markers and disease stage in colorectal cancer patients.** <u>Kilic</u> <u>L</u>¹, <u>Yildiz I</u>², <u>Sen FK</u>², <u>Erdem MG</u>³, <u>Serilmez M</u>⁴, <u>Keskin S</u>², <u>Ciftci</u> <u>R</u>², <u>Karabulut S</u>², <u>Ordu C</u>⁵, <u>Duranyildiz D</u>⁴, <u>Tas F</u>².

<u>Ann Surg Oncol.</u> 2013 Sep;20(9):2908-13. doi: 10.1245/s10434-013-2968-8. Epub 2013 Apr 25. **Preoperative plasma hyperfibrinogenemia is predictive of poor prognosis in patients with nonmetastatic colon cancer.**<u>Son HJ</u>¹, <u>Park JW</u>, <u>Chang HJ</u>, <u>Kim DY</u>, <u>Kim BC</u>, <u>Kim SY</u>, <u>Park</u> <u>SC</u>, <u>Choi HS</u>, <u>Oh JH</u>. Man YN, Wang YN, Hao J, et al. **Pretreatment plasma D-dimer, fibrinogen, and platelet levels significantly impact prognosis in patients with epithelial ovarian cancer independently of venous thromboembolism**. *Int J Gynecol Cancer*. 2015;25(1):24-32.

Kilic L, Yildiz I, Sen FK, et al. **D-dimer and international normalized ratio (INR) are correlated with tumor markers and disease stage in colorectal cancer patients**. *Cancer Biomark*. 2015;15(4):405-411.



1. HYPERCOAGULATION

Interventions

Curcumin 1-6 g/day



Curcumin, a polyphenol possesses antiinflammatory, antiproliferative, antiangiogenic and **anticoagulant activities.** Curcumin and bisdemethoxycurcumin (BDMC) **showed anticoagulant effect in vivo**. Data showed that curcumin and bisdemethoxycurcumin BDMC **prolonged PTT and PT significantly and inhibited thrombin** and activated Factor X (Fxa) activities.

BMB Rep. 2012 Apr;45(4):221-6. Anticoagulant activities of curcumin and its derivative. Kim DC1, Ku SK, Bae JS.

Resveratrol and Thrombosis

- Reduces platelet activation and aggregation
- Reduces synthesis of prothrombotic eicosanoid mediators
- Decreases gene expression of tissue factor
- Inhibits the generation of reactive oxygen species
- Reduces fibrinogen levels
- Increases fibrinolysis
- Decreases plasma homocysteine

Antiplatelet properties of natural products

Vilahur G, Badimon L. Antiplatelet properties of natural products. Vascul Pharmacol. 2013 Sep-Oct;59(3-4):67–75.



1-5g/day


Reduces platelet aggregation and activation

Reduces P-selectin expression

Inhibits COX 2, LOX5, PGE2, IL1, IL6, TNFa, CRP

Inhibits Angiogenesis and VEGF

Reduces endothelial cell adhesion

Omega-3 Fatty Acids and Thrombosis Semin Thromb Hemost. 2013 Feb;39(1):25-32. Effects of omega-3 polyunsaturated fatty acids on platelet function in healthy subjects and subjects with cardiovascular disease. McEwen et al

Atherosclerosis. 2013 Feb;226(2):328-34. doi:

10.1016/j.atherosclerosis.2012.10.056. Influence of omega-3 poly unsaturated fatty acid-supplementation on platelet aggregation in humans: a metaanalysis of randomized controlled trials.Gao LG et al

Ren Shen | Panax Ginseng Regulates Angiogenesis and Thrombosis 1-3g/day

Ginsenoside Rp1 inhibits platelet activation and thrombus formation and MAPK activation

Decreases thrombin & platelet aggregation

Phytotherapies: Efficacy, Safety, and Regulation edited by Iqbal Ramzan John Wiley & Sons, Apr 17, 2015 -pp257-58

Ginsenoside Rg1 inhibits platelet activation and arterial thrombosis, Thromb Res. January 2014 Volume 133, Issue 1, Pages 57–65 <u>Qi Zhou</u>, et al,

Salvia miltiorrhiza | Dan Shen and Thrombosis



Primary Active Consituents 1-3 g/day Salvianolic acid Acetyl Salvianolic Acid Tanshinone IIa Cryptotanshinone

- Inhibits platelet aggregation & activation
- Inhibits thrombus formation
- Reduces leukocyte-endothelial adherence
- Inhibits Thromoboxane B2, COX1 COX2 NOX1 NOX2 NOX4
- Inhibits MMP matrix metalloproteases
- Inhibits P13K kinase pathway

Salvia miltiorrhiza | Dan Shen and Thrombosis



J Thromb Haemost. 2010 Jun;8(6):1383-93. doi: 10.1111/j.1538-7836.2010.03859.x. Epub 2010 Mar 19. Salvianolic acid A inhibits platelet activation and arterial thrombosis via inhibition of phosphoinositide 3-kinase.<u>Huang_et al</u> <u>Thromb Res.</u> 2010 Jul;126(1):e17-22. Antiplatelet and antithrombotic activities of salvianolic acid A. <u>Fan HY</u> et al

Summary : Monitor All Patients for Signs of Thrombosis & Active Coagulation

Screen patients >45 yo and with risk factors for early identification of signs of potential malignancy

Monitor patients in treatment for risk of VTE & PE

Monitor patients living with cancer as a chronic illness for signs of progression

Monitor patients in remission (NED) for signs of recurrence

2. COPPER & ANGIOGENESIS

Angiogenesis: A Copper Dependent Process

Therapeutic Copper Depletion: Anti-Angiogenic & Anti-Metastatic

ANGIOGENESIS

- Normal physiological process through which new blood vessels form from preexisting vessels
- Present in normal growth and development and wound healing
- Fundamental step in the transition of tumors from a benign state to a malignant state
- Promotes tumor growth and metastasis



https://www.behance.net/gallery/11816509/Tumor-Angiogenesis-Infographic-Colorectal-Cancer



REVIEW Front. Oncol., 03 July 2012 **Cornering metastases:** therapeutic targeting of circulating tumor cells and stem cells

Metastasis the development of secondary malignant growths at a distance from a primary site of the cancer



Clin Exp Pharmacol Physiol. 2009 Jan;36(1):88-94. **Copper and angiogenesis: unravelling a relationship key to cancer progression.** Finney L1, Vogt S, Fukai T, Glesne D.

Angiogenesis displays an exquisite sensitivity to bioavailable copper

Depletion of copper has been shown to inhibit angiogenesis in a wide variety of cancers

Inhibition of Angiogenesis & Metastasis

- Copper is one of the key components of enzymes that control the tumor microenvironment, as well as appearing to have a role in how cancer cells migrate.
- Copper depletion inhibits angiogenesis (formation of new blood supply to tumor) and metastasis (cancer cell migration).
 Clin Exp Pharmacol Physiol. 2009 Jan;36(1):88-94.

J Trace Elem Med Biol. 2014 Oct;28(4):372-8. 2014 Aug 10. Brewer GJ1. The promise of copper lowering therapy with tetrathiomolybdate in the cure of cancer and in the treatment of inflammatory disease.

- The study showed major efficacy of TM against advanced human cancers, heretofore virtually incurable, particularly if the cancer has been reduced to no evidence of disease (NED) status....
- Where the remaining disease is micrometastatic, TM therapy appears to be CURATIVE

J Trace Elem Med Biol. 2014 Oct;28(4):372-8. 2014 Aug 10. Brewer GJ1. The promise of copper lowering therapy with tetrathiomolybdate in the cure of cancer and in the treatment of inflammatory disease.

 TM also has major anti-inflammatory properties by inhibiting copper dependent cytokines involved in inflammation.

 This anti-inflammatory effect may be involved in TM's anti-cancer effect because cancers, as they advance, attract inflammatory cells that provide a plethora of additional proTetrathiomolybdate-associated copper depletion decreases circulating endothelial progenitor cells in women with breast cancer at high risk of relapse



Ann Oncol (2013) 24(6): 1491-1498. Jain,S, Vahdat, LT et al Patients who were at high risk of cancer recurrence and received copper depletion therapy - in the form of the drug tetrathiomolybdate (TM) experienced **an overall increase in survival time as well as a decreased risk of relapse.** Clin Cancer Res. 2016 Oct 21. 1326.2016. Chan N, Vahdhat, L et al

Influencing the Tumor Microenvironment: Phase 2 study of copper depletion with tetrathiomolybdate in high risk breast cancer and preclinical models of lung metastases

75 pts enrolled; 51 pts completed 2 years (1396 cycles). Stage 2 triple negative BC (TNBC), Stage 3 and stage 4 without any evidence of disease, (NED) BC pts, received oral TM to maintain ceruloplasmin (Cp) between 8-17mg/dL for 2 years or until relapse.

Clin Cancer Res. 2016 Oct 21. 1326.2016. Chan N, Vahdhat, L et al Influencing the Tumor Microenvironment: Phase 2 study of copper depletion with tetrathiomolybdate in high risk breast cancer and preclinical models of lung metastases

2 year EFS for stage 2-3 and stage 4 NED was 91% and 67%, respectively. For TNBC pts EFS 90% (adjuvant pts) and 50% (stage 4 NED pts) at a median follow-up of 6.3 years. In preclinical models, TM decreased metastases to lungs (p=0.04), LOX activity (p= 0.03) and collagen crosslinking (p=0.012). J Trace Elem Med Biol. 2014 Oct;28(4):372-8 The promise of copper lowering therapy with tetrathiomolybdate in the cure of cancer and in the treatment of inflammatory disease. Brewer GJ

Clin Cancer Res. 2000 Jan;6(1):1-10. **Treatment of metastatic cancer with tetrathiomolybdate, an anticopper, antiangiogenic agent: Phase I study.**Brewer GJ, Merajver SD et al

Integr Cancer Ther. 2002 Dec;1(4):327-37. Cancer therapy with tetrathiomolybdate: antiangiogenesis by lowering body copper--a review. Brewer GJ, Merajver SD.

The Role of Copper in the Angiogenesis Process, Dwight L. McKee, M.D. (unpub)

Denoyer D, Masaldan S, La Fontaine S, Cater MA**. Targeting copper in cancer therapy: 'Copper That Cancer**'. *Metallomics*. 2015;7(11):1459-1476. [abstract

ORAL COPPER DEPLETION

Nutraceuticals

Tetrathiomolybdate

Control Copper Intake

Normal Laboratory Values

Goals for Inhibition of Angiogenesis Goal Serum Copper 72-166 ug/dl (72-95) Ceruloplasmin 16-39 mg/dl (10-22) Serum Zinc 56-134 ug/dl

Zn: Cu Ratio at least > 1:1 Better 2:1-3:1

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Copper Depletion |Tetrathiomolybdate

TM Dose: 20-40 mg po with each meal plus 60 mg po at bedtime on empty stomach

Monitor Serum Cp, Cu, Zn and CBC q 2-4 weeks

Target Goals:

<u>Cp and Cu lowest quartile of normal</u> (do not chelate to below 10mg/dl) <u>Zn:Cu Ratio 3:1 - 2:1</u>

Requires Oral Zn Supplementation (60-120mg/day) as Zinc citrate or picolinate

Copper Depletion: Nutraceuticals Sulfhydryl Containing Compounds EMPTY STOMACH

- N-Acetylcysteine 500-1000mg qid
- Alpha Lipoic Acid 100mg qid

WITH FOOD

- Zinc Citrate or Picolinate 30-120/mg/d
- Control Copper Intake: Avoid liver, organ meats, oysters, copper cookware, copper containing supplements

,.....

Top 10 Foods Highest in Copper

0.9mg of Copper = 100% of the Daily Value (%DV)



https://www .myfooddat a.com/print ables/highcopperfoodsprintable.p ng

Eat in Moderation



3. VITAMIN D

Modulates Carcinogenesis and Progression

Low Vitamin D Levels Correlated with Increased Cancer Risk and Poor Prognosis

Optimal Levels Associated with Reduced Recurrence & Reduced Mortality

Vitamin D and Cancer: A review of molecular mechanisms Biochem J. 2012 Jan 1; 441(1): 61–76.

- Regulates Gene Transcription
- Induces Growth Arrest
- Induces Apoptosis
- Enhances DNA Repair
- Enhances Antioxidant Protection
- Enhances Immune Modulation
- Enhances Differentiation
- Decreases Pro-Inflammatory Cytokines
- Decreases Invasion into the ECM
- Decreases Angiogenesis & Metastasis

Oncol Res. 2014;22(3):129-37.. **Role of Vitamin D Metabolism and Activity on Carcinogenesis**. Wu X1, et al

Increased circulating levels of vitamin D are associated with reduced occurrence and a reduced mortality in different histological types of cancer, including those resident in the skin, prostate, breast, colon, ovary, kidney, and bladder.

Vitamin D status may be an important modulator of cancer progression in persons living with cancer.

Endocrinology. 2016 Apr;157(4):1341-7.

Tumor Autonomous Effects of Vitamin D Deficiency Promote Breast Cancer Metastasis. Williams JD, et al

Patients with breast cancer frequently have preexisting vitamin D deficiency (low serum 25-hydroxyvitamin D) when their cancer develops.

A number of epidemiological studies show an inverse association between BCa risk and vitamin D status in humans.

Several studies have reported that **BCa patients with** vitamin D deficiency have a more aggressive molecular phenotype and worse prognostic indicators.

J Clin Endocrinol Metab. 2014 Jul;99(7):2327-36. Li, M, Chen, P et al Review: the impacts of circulating 25hydroxyvitamin D levels on cancer patient outcomes: a systematic review and meta-analysis Meta-analysis: 25 studies with 17,332 cases. Significant associations between circulating 25(OH)D levels at or near the time of diagnosis and the outcomes for cancer patients were found.

Cancer patients with higher circulating 25(OH)D levels at or near the time of diagnosis have better outcomes.

J Clin Endocrinol Metab. 2014 Jul;99(7):2327-36. Li, M, Chen, P et al

The pooled hazard ratio for the highest vs the lowest quartile of circulating 25(OH)D levels was 0.55 (95% confidence interval [CI] = 0.33-0.91) for overall survival of colorectal cancer patients, 0.63 (95% CI = 0.51-0.77) for breast cancer patients, and 0.48 (95% CI = 0.36-0.64) for lymphoma patients.

Higher 25(OH)D levels were significantly associated with reduced cancer-specific mortality for patients with colorectal cancer (P = .005) and lymphoma (P < .001) and improved disease-free survival for patients with breast cancer (P < .001) or lymphoma (P < .05).

A 10-nmol/L increment in circulating 25(OH)D levels conferred a hazard ratio of 0.96 (95% CI = 0.95-0.97) for <u>overall survival of the cancer patients</u>.

Li M, Chen P, Li J, Chu R, Xie D, Wang H. **Review: the impacts of circulating 25-hydroxyvitamin D levels on cancer patient outcomes: a systematic review and metaanalysis**. *J Clin Endocrinol Metab*. 2014;99(7):2327-2336. [abstract]

Peña C, García JM, Silva J, et al. E-cadherin and vitamin D receptor regulation by SNAIL and ZEB1 in colon cancer: clinicopathological correlations. *Hum Mol Genet*. 2005;14(22):3361-3370. [abstract]

Wang D, Vélez de-la-Paz OI, Zhai JX, Liu DW. **Serum 25hydroxyvitamin D and breast cancer risk: a meta-analysis** of prospective studies. *Tumour Biol.* 2013;34(6):3509-3517. [abstract]

J Clin Oncol. 2009 Aug 10;27(23):3757-63 **Prognostic Effects of 25-Hydroxyvitamin D** Levels in Early Breast Cancer

Vitamin D deficiency may be associated with poor outcomes in breast cancer.

Cohort of 512 women diagnosed with early breast cancer Mean follow up was 11.6 years

Women with deficient and insufficient levels had increased rates of recurrence and death when compared to women with sufficient levels

J Clin Oncol. 2009 Aug 10;27(23):3757-63 **Prognostic Effects of 25-Hydroxyvitain D** Levels in Early Breast Cancer

VITAMIN D LEVELS 25 HYDROXY D

| Deficient | Optimal | Treat Cancer and Heart Disease | Excess |
|-----------|---------|-----------------------------------|--------|
| < 50 | 50-70 | 70-100 | > 100 |
| ng/ml | ng/ml | ng/ml | ng/ml |

Multiply ng/ml by 2.5 to convert to nmol/litre

25-OH VITAMIN D TARGET 65-80 NG/ML *OPTIMZED 75 NG/ML*

Oral Cholecalciferol VITAMIN D3 2,000iu - 10,000iu = 50 mcg-250 mcg daily

Dietary Sources of Vitamin D



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4. INFLAMMATION

C-Reactive Protein Neutrophil-Lymphocyte Ratio
CANCER-RELATED INFLAMMATION PROMOTES:

- Tumor Growth
- Proliferation
- Angiogenesis
- Metastasis
- Immune Suppression
- Cancer Related Fatigue
- Depression
- Pain



Courtesy of Jeanne Wallace Ph.D.

Inflammation & Cancer Survival

Survival of Cancer Patients Correlated to the Level of Inflammation





www.biooncology.com/molecular-causes-of-cancer/inflammation?intc=rrmolecular-causes-of-cancer

Nuclear Factor kappa-B and Tumorigenesis Master Regulator of Inflammation





Curr Opin Pharmacol. 2009 Aug ; 9(4): 351-369. Aggarwal.B et al



INFLAMMATION: C-REACTIVE PROTEIN

TARGET 1.0-3.0 mg/L

Prognostic Marker in A Wide Variety of Cancers Increased Risk of Carcinogenesis, Angiogenesis, Metastasis, Advanced Stage, Mortality Poor Prognosis

Curr Opin Pharmacol. 2009 August ; 9(4): 351 369. Inflammation and Cancer: How Friendly Is the Relationship For Cancer Patients? B.B. Aggarwal

CRP is emerging as an important prognostic marker in a wide variety of cancers.

C-reactive protein (CRP), an NF- B-regulated gene product has been **linked with prognosis** of cancers of the breast, colon, kidney, ovary, lung and stomach, and multiple myeloma, melanoma, and non-Hodgkin's lymphoma.

Crit Rev Clin Lab Sci. 2011 Jul-Aug;48(4):155-70 Elevated C-reactive protein in the diagnosis, prognosis, and cause of cancer. Allin KH et al.

Among individuals diagnosed with cancer during the study period, **individuals with a high baseline CRP (>3 mg/L) had an <u>80% greater risk of early</u> <u>death</u> compared with those with low CRP levels (<1 mg/L).**

Patients with invasive breast cancer and CRP levels>3 mg/L at diagnosis had a <u>1.7-fold</u> increased risk of death from breast cancer compared to patients with CRP levels<1 mg/L at diagnosis.

INFLAMMATION: NEUTROPHIL-LYMPHOCYTE RATIO (NLR)

Prognostic Progression Free Survival Overall Survival NLR>4 Poor Prognosis

Prognostic Role of Neutrophil-to-Lymphocyte Ratio in Solid Tumors: A Systematic Review and Meta-Analysis

- One hundred studies comprising 40,559 patients were included in the analysis, 57 of them published in 2012 or later
- Median cutoff for NLR was 4.
- Overall, NLR greater than the cutoff was associated with a hazard ratio for OS of 1.81 (95% CI = 1.67 to 1.97; P < .001), an effect observed in all disease subgroups, sites, and stages.

JNCI J Natl Cancer Inst (2014) 106(6): dju124 doi:10.1093/jnci/dju124 Neutrophils and other cells such as macrophages have been reported to secrete tumor growth-promoting factors, including

- VEGF vascular endothelial growth factor
- hepatocyte growth factors
- IL-6
- IL-8
- MMP matrix metalloproteinases and
- Elastases

and thus likely contribute to a stimulating tumor microenvironment.

JNCI J Natl Cancer Inst (2014) 106(6): dju124 doi:10.1093/jnci/dju124

Prognostic Role of Neutrophil-to-Lymphocyte Ratio in Solid Tumors: A Systematic Review and Meta-Analysis

In summary, a high Neutrophil to Lymphocyte Ratio (NLR >4.0) is associated with adverse survival in many solid tumors, and NLR may serve as a cost-effective prognostic biomarker.

JNCI J Natl Cancer Inst (2014) 106(6): dju124 doi:10.1093/jnci/dju124



INFLAMMATION CONTROL

Curcuma Longa Curcuminoids Omega-3 Fatty Acids Probiotics Scutellaria baicalensis Baicalein polyphenol Berberine isoquinoline alkaloid Tocotrienols

ONCO-INFLAMMATION CONTROL

Curcuminoids

O-3 FA EPA DHA

Probiotics

Baicalein polyphenol

Berberine alkaloid

<u>Tocotrienols</u>

COX 2, NFkB, TNFa, IL6, IL1 COX 2, LOX5, PGE2, IL1, IL6, TNFa, CRP TNFa, IL6, IL 10, NFkB TNFa IL-6 IL-1 NFkB COX-2

IL-6 TNFa IL-1

TNFa NFkB IL1 IL6 IL8 12-LOX PGE-2

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Trends Pharmacol Sci. 2009 Feb;30(2):85-94. **Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets.** Aggarwal BB1, Sung B.

Curcumin mediates its anti-inflammatory effects through the downregulation of inflammatory transcription factors (such as nuclear factor kappaB), enzymes (such as cyclooxygenase 2 and 5 lipoxygenase) and cytokines (such as tumor necrosis factor, interleukin 1 and interleukin 6







Down-regulate Inflammation IL1 IL6 TNFa CRP COX 2 LOX5 PGE2 2g-6g/day

Adv Food Nutr Res. 2012;65:211-22 Health benefits of n-3 polyunsaturated fatty acids: eicosapentaenoic acid and docosahexaenoic acid. Siriwardhana N et al

ntrol

PROBIOTICS and Inflammation Control

Down-Regulate Pro-Inflammatory Cytokines TNFa IFNg IL-12 IL6 NFkB

Up-Regulate Anti-Inflammatory Cytokines IL-10



Curr Opin Gastroenterol. 2007;23(6):679-692. The Mechanism of Action of Probiotics Monica Boirivant, Warren Strober

Am J Clin Nutr June 2001 vol. 73 no. 61142S-1146S Probiotics in Human Disease E.Isolauri

Baicalein (polyphenol) Scutellaria baicalensis Huang Qin

> inhibits TNFa IL-6 IL-1 NFkB COX-2

1-3g/day



Polyphenols in Human Health and Disease ed. Ronald Ross Watson, Victor R. Preedy, Sherma Zibad pp 398-399

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Berberine

isoquinoline alkaloid Down-regulates IL-6 TNFa IL-1

Berberis aquifolium Berberis vulgaris Coptis chinensis Hydrastis canadensis Phellodendron amurense 500-1000mg tid







Arch Biochem Biophys. 2014 Oct 1;559C:91-99 **Downregulation of TNF tumor necrosis factor and other proinflammatory biomarkers by polyphenols.** Gupta SC,, Aggarwal BB. et al

Endocrine. 2008 Jun;33(3):331-7 Berberine inhibits the expression of TNFalpha, MCP-1, and IL-6 in AcLDL-stimulated macrophages through PPARgamma pathway. Chen FL et al

American Journal of Physiology - Endocrinology and Metabolism 1 April 2009 Vol. 296 no. 4,E955-E964 Berberine suppresses proinflammatory responses through AMPK activation in macrophages Hyun Woo et al

Tocotrienols exhibit stronger antioxidant and anti-inflammatory activities compared to alpha-tocopherol

TOCOTRIENOLS SUPPRESS

125-250mg bid

- Expression of Mediators of Inflammation: TNFa, NFkb, IL1, IL6, IL8 ,COX2, 12-LOX PGE-2
- STAT 3 Signaling
- Glutamate induced neurotoxicity
- Arachidonic Acid induced inflammation and oxidative stress

<u>Ann N Y Acad Sci.</u> 2011 Jul;1229:18-22. doi: 10.1111/j.1749-6632.2011.06088.x.

Tocotrienols: inflammation and cancer.

<u>J Neuroinflammation.</u> 2016 Jun 14;13(1):148. doi: 10.1186/s12974-016-0615-6. **Rice bran derivatives alleviate microglia activation: possible involvement of MAPK pathway.** <u>Bhatia HS</u>^{1,2}, <u>Baron J</u>³, <u>Hagl S</u>⁴, <u>et al</u>

Tocotrienols, the Vitamin E of the 21st Century It's Potential Against Cancer and Other Chronic Diseases

• Found in rice bran and palm oil

125-250mg bid

- Four isomers: alpha, beta, gamma, delta
- Most potent forms of tocotrienols are delta and gamma
- Separate dosing from tocopherol supplements for best assimilation and utilization
- Tocopherols may interfere with the actions of tocotrienols
- No known adverse effects when consumed as part of a normal diet

Biochem Pharmacol. 2010 December 1; 80(11): 1613–1631. BB. Aggarwal, et al

5. INSULIN RESISTANCE AND OBESITY

Obesity is the strongest link between cancer and diabetes

CA Cancer J Clin. 2010 Jul-Aug;60(4):207-21. **Diabetes and cancer: A Consensus Report.** Giovannucci E, et al

Biomarkers of Insulin Resistance

- Fasting Glucose > 100mg/dl
- HgbA1c > 5.6 (goal 4.8-5.2)
- Fasting Insulin > 3.16 uIU/mI or
- Fasting Glucose: Fasting Insulin ratio < 4.5
- HOMA-IR > 2.5 = Fasting Insulin:Fasting Glucose
- Visceral Adiposity
- Elevated Triglycerides > 150mg/dl
- Waist Circumference > 40 in (101cm) in men and
 35 in (80cm) in women

HOMA-IR: Homeostatic Model Assessment of Insulin Resistance HOMA-IR Calculation Fasting Insulin (mU/L) X Fasting Glucose (mg/dL) = HOMA-IR

Normal Healthy Function: 1.0 (0.5–1.4) Less than 1.0 normal insulin sensitivity Above 1.9 early insulin resistance Above 2.9 significant insulin resistance ©American Institute of Integrative Oncology www.aiiore.com





Diabetes Obes Metab. 2014 Feb;16(2):97-110. Garg SK et al



Cancers Associated with Diabetes Hyperglycemia Hyperinsulinemia

Pancreatic

Gastric Esophageal **Colorectal**

Liver Gall Bladder Breast

Ovarian

Uncertain Link

Lung Cancer

Endometrial Cervical Urinary Bladder Renal Multiple Myeloma Non-Hodgkins Lymphoma

<u>Conflicting Studies</u> Prostate Fasting Glucose 70-90

HGBA1C 4.5-5.2

BMI 18.5-22.9

Diab Care. 2010 Jul; 33(7): 1674–1685. Diabetes and Cancer: A Consensus Report

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Insulin is a Growth Factor

Elevated levels of insulin have been shown to be a risk factor for a number of cancers.

Diabetes Obes Metab. 2014 Feb;16(2):97-110. Garg SK et al

Most, if not all, tumor cells have a high demand on glucose compared to benign cells of the same tissue and conduct glycolysis even in the presence of oxygen (the Warburg effect).

In addition, many cancer cells express insulin receptors (IRs) and show hyperactivation of the IGF1R-IR pathway.

Evidence exists that chronically elevated blood glucose, insulin and IGF1 levels facilitate tumorigenesis and worsen the outcome in cancer patients.

Diabetes Obes Metab. 2014 Feb;16(2):97-110. Garg SK1, Maurer H, Reed K, Selagamsetty R.

Obesity A Major Risk Factor for Cancer

©American Institute of Integrative Oncology

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Obesity May Account for 14% of **All Cancer Deaths** in Men and 20% in Women

Anand P, Kunnumakkara et al. Cancer is a preventable disease that requires major lifestyle changes. Pharm. Res. 2008;25:2097-2116.

OBESITY is a Risk Factor for Cancer

<u>Cancers Consistently</u> <u>Associated with Obesity</u> Breast Endometrial Colorectal Pancreas Esophageal Renal Cell Liver

Diabetes and Cancer: An AACE/ACE Consensus Statement.

Endocrine Practice: July 2013, Vol. 19, No. 4, pp. 675-693., Yehuda Handelsman, et al



Cancer is a Preventable Disease that Requires Major Lifestyle Changes.

Pharmaceutical Research, (2008). 25(9), 2097–2116.
American Society of Clinical Oncology Position Statement on Obesity and Cancer JCO November 1, 2014 vol. 32 no. 31 3568-3574

A recent meta-analysis of 82 studies including • more than 200,000 patients with breast cancer demonstrated a 75% increase in mortality in premenopausal women and a 34% increase in mortality in postmenopausal women who were obese at the time of breast cancer diagnosis, as compared with patients who were of normal weight at diagnosis.

American Society of Clinical Oncology Position Statement on Obesity and Cancer JCO November 1, 2014 vol. 32 no. 31 3568-3574

- Obese men seem to be at increased risk of developing biologically aggressive prostate cancers and also are more likely to have advanced disease at the time of prostate cancer diagnosis.
- A BMI ≥ 35 kg/m2 may be associated with an increased risk of colon cancer recurrence and mortality
- Emerging data suggest that obesity may be a prognostic factor in other malignancies

INSULIN RESISTANCE OBESITY | CANCER RISK INTERVENTIONS

- Curcumin
- Omega-3 Fatty Acids
- Ganoderma lucidum
- EGCg Green Tea Catechin
- Resveratrol
- Tocotrienols

CURCUMIN DIRECTLY INHIBITS THE TRANSPORT ACTIVITY OF GLUT1

The observation that curcumin directly inhibits the transport activity of GLUT1 is also potentially an additional mechanism for the documented anti-cancer effects of curcumin. Many cancers are highly glycolytic and overexpress GLUT1. A direct inhibition of GLUT1 would be expected to slow glucose uptake. Biochimie. 2016 Jun; 125: 179–185., Leesha K. et al

Perrone D, Ardito F, Giannatempo G, Dioguardi M, Troiano G, Lo Russo L, DE Lillo A, Laino L, Lo Muzio L. **Biological and therapeutic activities, and anticancer properties of curcumin**. Exp Ther Med. 2015;10:1615–1623.

Vallianou NG, Evangelopoulos A, Schizas N, Kazazis C. **Potential anticancer properties and mechanisms of action of curcumin**. Anticancer Res. 2015;35:645–651

Furuta E, Okuda H, Kobayashi A, Watabe K. **Metabolic genes in cancer: their roles in tumor progression and clinical implications**. Biochim Biophys Acta. 2010;1805:141–152.

Szablewski L. Expression of glucose transporters in cancers. Biochim Biophys Acta. 2013;1835:164–169.

Mol Nutr Food Res. 2013 Sep;57(9):1569-77. Na LX, Li Y, et al Curcuminoids exert glucose-lowering effect in type 2 diabetes by decreasing serum free fatty acids: a double-blind, placebo-controlled trial.

Curcuminoids (300 mg/d x 3 months) Significantly decrease:

- Fasting Blood Glucose (p < 0.01)
- HgbA1c (p = 0.031)



- Insulin Resistance Index (HOMA-IR) (p < 0.01)
- Serum Total FFAs (p < 0.01)
- Triglycerides (P = 0.018)

Annu Rev Nutr. 2010 Aug 21; 30: 173–199. Bharat B. Aggarwal Targeting Inflammation-Induced Obesity and Metabolic Diseases by Curcumin and Other Nutraceuticals

- Curcumin-induced alterations reversed insulin resistance, hyperglycemia, hyperlipidemia, and other symptoms linked to obesity.
- Other structurally homologous nutraceuticals derived from red chili, cinnamon, cloves, black pepper, and ginger, also exhibit effects against obesity and insulin

Omega-3 fatty acids reduce obesity-induced tumor progression



Obesity and inflammation are both risk factors for a variety of cancers, including breast cancer in postmenopausal women.

Intake of omega-3 polyunsaturated fatty acids (-3 PUFAs) decreases the risk of breast cancer, and also reduces obesity-associated inflammation and insulin resistance

Oncogene. 2015 Jul; 34(27): 3504–3513. Heekyung Chung, et al

Diabetes and Inflammation

Both type 1 and type 2 diabetes are associated with increased blood concentrations of several inflammatory biomarkers

- C-reactive protein (CRP)
- Interleukin 2 IL-2
- Interleukin-6 IL-6
- Tumour Necrosis Factor-alpha (TNF-)

O-3 Fatty Acids Lower Diabetes Associated Inflammation Study doses: 2.7 - 4.0 grams/day Biochim Biophys Acta. 2015 Apr;1851(4):469-84 Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance. Calder PC

Lipids Health Dis. 2016 Aug 20;15:133. What is the impact of n-3 PUFAs on inflammation markers in Type 2 diabetic mellitus populations?: a systematic review and meta-analysis of randomized controlled trials. Lin N, et al

Anti-Diabetic & Anti-Obesogenic Effects of Polysaccharides from Aqueous Extract Ganoderma lucidum (Reishi Mushroom)



- Reduction of Body Weight and Fat Accumulation
- Modulation of Gut Bacteria
- Maintenance of Intestinal Integrity & Tight Junctions
- Increased Production of SCFA in Intestines
- Delayed Gastric Emptying>Reduced Appetite
- Reduced expression of TNFa, IL1B1, IL6
- Improved Glucose Tolerance & Insulin Sensitivity

2 - 6 grams per day

Nat.Rev.Endoc. 11. 577-591 September 2015 Short-chain fatty acids in control of body weight and insulin sensitivity Canfora.EE, et al.

Nat Rev Endocrin 16 Sept 2016 REVIEW: Anti-obesogenic and antidiabetic effects of plants and mushrooms Jan Martel, et al

Green Tea Catechins EGCg 1-3 g/day Normalizes Glucose & Insulin Metabolism





Int. J. Mol. Sci. 2012, 13(1), 579-595; Review: Nutraceutical Approach for Preventing Obesity-Related Colorectal and Liver Carcinogenesis Masahito Shimizu, et al.

Am J Clin Nutr. 2008 Mar;87(3):778-84.

Green tea extract ingestion, fat oxidation, and glucose tolerance in healthy humans.

Venables MC, et al.

Tocotrieinols Improve Insulin Sensitivity

125-250mg bid

- Tocotrienols participate in important biochemical mechanisms related to the onset of diabetes and obesity.
- Tocotrienols act by regulation of gene expression, signal transduction, and modulation of cell functions.
- The tocotrienol-rich fraction of palm oil improved whole body glucose utilization and insulin sensitivity by selectively regulating PPAR target genes.

Int J Mol Sci. 2016 Oct 20;17(10). pii: E1745.

Tocopherols and Tocotrienols in Common and Emerging Dietary Sources: Occurrence, Applications, and Health Benefits. <u>Shahidi F1, de Camargo AC</u>^{2,3} <u>Mol Nutr Food Res.</u> 2010 Mar;54(3):345-52. doi: 10.1002/mnfr.200900119. **Vitamin E tocotrienols improve insulin sensitivity through activating peroxisome proliferator-activated receptors.** <u>Fang F1</u>, <u>Kang Z</u>, <u>Wong C</u>. (Murine study)

Grape Resveratrol Increases Serum Adiponectin and Down-regulates Inflammatory Genes 1000-5000mg/day

Significantly decreases inflammatory factors High-sensitivity C-reactive protein (-26%,p = 0.03), Tumor necrosis factor- α (-19.8%, p = 0.01), Plasminogen activator inhibitor type 1 (-16.8%, p = 0.03) Interleukin-6/interleukin-10 ratio (-24%, p = 0.04) Decreases fasting glucose, insulin, A1C and insulin resistance

Increases anti-inflammatory Interleukin-10 (19.8%, p = 0.00) and Adiponectin (6.5%, p = 0.07)



World J Diabetes 2016 April 10; 7(7): 142-152 **Novel nutraceutic therapies for the treatment of metabolic syndrome** Esperanza Martínez-Abundis Cardiovasc Drugs Ther. 2013 Feb;27(1):37-48 Tomé-Carneiro J.et al

Selected References: Cancer Risk Reduction in Obese Patients

Shanmugalingam T, Crawley D, Bosco C, et al. **Obesity and cancer: the role of vitamin D**. *BMC Cancer*. 2014;14712. [abstract]

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Joshu CE, Prizment AE, Dluzniewski PJ, et al. **Glycated hemoglobin and cancer incidence and mortality in the Atherosclerosis in Communities** (ARIC) Study, 1990-2006. *Int J Cancer*. 2012;131(7):1667-1677. [abstract]

Emerging RFC, Seshasai SR, Kaptoge S, et al. **Diabetes mellitus, fasting glucose, and risk of cause-specific death**. *N Engl J Med*. 2011;364(9):829-841. [abstract]

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Renehan AG, et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008;371(9612):569-578. [abstract]

Calle EE, et al Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med*. 2003;348(17):1625-1638. [abstract]

Mazzarella L. Why does obesity promote cancer? Epidemiology, biology, and open questions. Ecancermedicalscience. 2015;9554. [abstract

Selected References: Cancer Risk Reduction Patients with Diabetes

Giovannucci E,, et al. **Diabetes and cancer: a consensus report**. *CA Cancer J Clin*. 2010;60(4):207-221. [abstract]

Noto H, et al. Significantly increased risk of cancer in patients with diabetes mellitus: a systematic review and meta-analysis. *Endocr Pract.* 2011;17(4):616-628. [abstract]

Xu CX, Zhu HH, Zhu YM. **Diabetes and cancer: Associations**, **mechanisms**, and **implications for medical practice**. *World J Diabetes*. 2014;5(3):372-380. [abstract]

Giovannucci E. Insulin, insulin-like growth factors and colon cancer: a review of the evidence. *J Nutr*. 2001;131:3109S-20S. [abstract]

Mol Nutr Food Res. 2010 Mar;54(3):345-52. doi: 10.1002/mnfr.200900119. Vitamin E tocotrienols improve insulin sensitivity through activating peroxisome proliferator-activated receptors. Fang F¹, Kang Z, Wong C.

SUMMARY

RECOMMENDATIONS: Use Selected Biomarkers to •Screen Patients > 45 yo and those with risk factors for early identification of signs of potential malignancy

 Monitor Patients Living with Cancer as a Chronic Illness for signs of progression

 Monitor Patients in Remission (NED) for signs of Recurrence

Lifestyle Interventions

- Anti-Thrombotic Anti-Inflammatory Diet
- Glycemic Control
- Regular Physical Activity
- Increase Lean Body Mass Decrease Fat
- Increase Fitness and Physical Activity
- Adequate Sleep
- Adequate Hydration
- Stop Smoking
- Support Self Care and Stress Management

Selected BioMarkers

- Fibrinogen activity
- D-Dimer
- Platelets
- WBC
- Copper
- Ceruloplasmin
- Zinc
- Zinc:Copper

- 25 OH Vitamin D
- hs-CRP
- Neutrophil:Lymphocyte
- IL-6
- Glucose
- HgbA1C
- IGF-1
- BMI

Materia Medica

- Curcumin
- Resveratrol
- Panax Ginseng
- Salvia Miltiorrhiza
- EGCg
- Baicalein
- Berberine
- Polyphenols
- Proteases

- Omega-3 Fatty Acids
- Zinc Citrate or Picolinate
- Vitamin D3
- N-Acetylcysteine
- Alpha Lipoic Acid
- Probiotics
- Tocotrienols
- Tetrathiomolybdate

Int J Mol Sci. 2013 Sep; 14(9): 17279–17303.





Q & A

Bonus: *What Common Blood Tests Reveal About Cancer Risk* http://aiiore.com/nanp2020

THANK YOU!

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