Laboratory Tests /Molecular Markers in Breast Cancer and Indicated Naturopathic Treatments

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Learning Objectives

• Understand established tumor markers for breast cancer (What and When)
• Define conventional laboratory measures that may help guide ND treatments decisions
• Review independent labs parameters that can help tailor treatment.
Overview of Cancerous Growth

1. **Normal cells**
   - Transformation: Activation of transcription factors (STAT3, AP-1, NF-k B)
   - Tumor Suppressor genes

2. **Tumor cells**
   - Proliferation: Overexpression of growth factors
     - Oncogenes: HER2, EGF/PDGF, Bcl-2, Cyclin D1

3. **Tumor Growth**
   - Invasion: Matrix metalloproteinases (COX-2), Adhesion Molecules, Cytokines/TNF, Angiogenic Factors

4. **Tumor metastasis**
Party Line-- ASCO

Tissue Derived Markers

• ER/PR receptor status
• Her2/neu
• uPA/PAI-1
• Oncotype Dx

Circulating Markers

• Ca 15-3
• Ca 27-29
• CEA

Predictive or Prognostic only; No screening markers recommended.
MUC1 FAMILY (Ca 15-3, 27-29)

Increased in 50-80% of metastatic Br Ca patients
Carcinoembryonic Antigen (CEA)

Structure of CEA protein (the 70-kD protein becomes 180 kD when glycosylated)

N domain

Glycosylation site

Disulphide bridge between cysteines

Schematic representation of the human carcinoembryonic antigen (CEA) gene and protein

Expert Reviews in Molecular Medicine © 2000 Cambridge University Press
When are they recommended?

- **ER/PR/ Her2/Neu**: all primary tumor samples

- **CEA/ Ca 15-3, 27-29**: Recommended for use in patients with established metastatic disease.  
  - NOT recommended for monitoring for recurrence

- **Oncotype DX**: Women with Stage I or II, ER positive, node negative invasive breast cancer (soon may be for node positive too)
Oncotype Dx- ER+, Node -

- 21 gene profile (measuring mRNA) to render a specific “recurrence score” (from 0-100)

- Used to assess the predictive benefit of chemotherapy in reducing distant mets in women who are taking tamoxifien for 5 years.
Oncotype DX™ Breast Cancer Assay uses RT-PCR to determine the expression of a panel of 21 genes in tumor tissue. The Recurrence Score™ is calculated from the gene expression results. The Recurrence Score range is from 0-100.

RESULTS

Recurrence Score = 15

Test results should be interpreted using the information in the Clinical Experience section below, which applies only to patients consistent with this clinical experience.

CLINICAL EXPERIENCE

Patients with a Recurrence Score of 15 in the clinical validation study had an Average Rate of Distant Recurrence at 10 years of 10% (95% CI: 7%-12%).

The following results are from a clinical validation study with prospectively-defined endpoints involving 688 patients. The patients enrolled in the study were female, stage I or II, node negative, ER/PR positive, and treated with tamoxifen. N Engl J Med 2004; 351: 2817-26.
Oncotype Dx

• Score below 18: Chemo not likely beneficial
• Scores between 18-31: We don’t know yet...
• Score 31-100: risk of distant recurrence is reduced by an absolute 28% with chemo (60% of women were without mets at 10 years with TAM only vs. 88% free of mets with TAM+CMF)

***When all Stage I and II breast cancer patients are pooled (scores 0-100), the absolute benefit of chemo on prevention of distant mets in 10 years is 4%.***
Genomic Signatures 
(DNA Microarray)

All look for *expressed genes* in the tumor cells

- Mammaprint® (Amsterdam 70-gene predictive profile) --- Fresh
- Oncotype Dx® (21-gene recurrence score) --- Fixed or Fresh
- 76-gene prognostic signature --- Fresh
- Wound response --- Fresh
- Two-gene ratio --- Fixed
Mammaprint

• FDA Approval for lymph node negative breast cancer patients under 61 years of age with tumors of less than 5 cm.
• Stratifies patient into “low risk” or “high risk” of distant metastasis
• Unlike Oncotype, the outcome of intervention (ie, chemo) has not been assessed
What ASCO has NOT Recommended

• Ki67, cyclin D, cyclin E, p27, p21, thymidine kinase, topoisomerase II, or other markers of proliferation to assign patients to prognostic groups.
• The above tests include tissue specimens as well as serum.

Circulating Markers
• Her2/neu serum
• Capthesin D
• Cyclin E fragments
• Proteomic Analysis
• Bone marrow micrometastasis tests
• Circulating Tumor Cells (CTC’s)
Serum HER-2/neu

**Serum HER-2/neu Test Utility**

**Metastatic Breast Cancer Diagnosis**

- **Serum HER-2/neu (baseline)**
  - Result $< 15$ ng/mL
  - Test Periodically
  - Serum HER-2/neu levels can become elevated in patients whose initial Serum HER-2/neu value is $< 15$ ng/mL

**Establish HER-2/neu Positivity**

- IHC/FISH Results from Primary Tumor Sample
  - **HER-2/neu Tissue Negative**
    - If Serum HER-2/neu level is $> 15$ ng/mL, additional testing of primary tumor or metastatic lesion by IHC/FISH may be warranted
  - **HER-2/neu Tissue Positive**
    - Candidate for HER-2/neu-targeted therapy

**Routine Monitoring**

- Decreasing levels reflect treatment response
- Increasing levels reflect disease progression
- A $> 20\%$ decrease in Serum HER-2/neu from pre- to post-treatment samples is associated with better clinical outcomes
Circulating Tumor Cells (CTC)

• Independent prognostic factor for distant mets free survival and Overall Survival (OS)
  – 115 pts with locally advanced operable Br Ca (f/u = 36 months)
  – 10% had >1CTC/7.5mL blood (before neoadjuvant chemo sample)

• reduced disease-free interval and overall survival, respectively, in node-negative breast cancer patients
  – 167 pts, node negative dz. Did correlate with Her2 +

Clinical Utility still being delineated...

Kaplan-Meier estimates of probabilities of progression-free survival and overall survival in patients with metastatic breast cancer for those with <5 CTCs per 7.5 mL of whole blood and those in the group with ≥5 CTCs in 7.5 mL of whole blood at the first follow-up visit after initiation of a new line of therapy (n=177 pts)

Hayes D F, Smerage J Clin Cancer Res 2008;14:3646-3650
Bone Marrow Micrometastasis aka Disseminated Tumor Cells (DTC’s)

<table>
<thead>
<tr>
<th>Tumor type (M0)</th>
<th>Detection rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>20-40</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>20-50</td>
</tr>
<tr>
<td>Lung cancer (NSCLC)</td>
<td>40-60</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>35-60</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>30-40</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>20-35</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>20-30</td>
</tr>
</tbody>
</table>

From Medscape:

“more than 30% of women with breast cancer have thousands of micrometastases in their bone marrow”

... less than half will have clinical metastasis.
In order to acquire mobility and invasiveness, carcinoma cells need to shed many features of their epithelial phenotype and undergo drastic alterations, acquiring the morphology and gene expression pattern of mesenchymal cells (Figure 1). This process, termed epithelial–mesenchymal transition (EMT), is physiologically used for wound healing in mature organisms and, importantly, is essential during early embryogenesis.
Overview of Cancerous Growth

Growth Factors:
- VEGF
- IGF

Pro-Inflammatory Molecules:
- NF Kappa B
- Cox-2

Cytokines:
- IL-6
- IL1B

Tumor Growth

Transformation

Activation of transcription factors
- STAT3
- AP-1
- NF-k B

Tumor Suppressor genes

Proliferation

Overexpression of growth factors
- Oncogenes
- HER2
- EGF/PDGF
- Bcl-2
- Cyclin D1

Invasion

Tumor metastasis

Matrix metalloproteinases
- COX-2

Adhesion Molecules
- Cytokines /TNF

Angiogenic Factors
Main proteins and genes in breast cancer are involved in a series of molecular interactions, which can result in cell proliferation. Among these proteins are variants, such as HER2 (a membrane growth factor receptor, similar to insulin-like growth factor 1 receptor (IGF-1R)).

**The Effects**

The signals activate specific genes, such as RAS, which give rise to proteins that act on additional genes. This series of gene-protein interactions, depicted in abbreviated form here, leads to cell growth and the suppression of mechanisms that would usually cause an abnormal cell to commit suicide. Mutations in any gene along such signaling pathways can produce similar results, making those genes and their encoded proteins therapeutic targets as well.

Like other growth factor receptors, estrogen receptor proteins dimerize when activated by estrogen. The receptor pair then acts directly on DNA (right) to switch on genes involved in cell growth and survival.
Growth Factors - General List

• Bone morphogenetic proteins (BMPs)
• Epidermal growth factor (EGF)
• Erythropoietin (EPO)
• Fibroblast growth factor (FGF)
• Granulocyte-colony stimulating factor (G-CSF)
• Granulocyte-macrophage colony stimulating factor (GM-CSF)
• Growth differentiation factor-9 (GDF9)
• Hepatocyte growth factor (HGF)
• Hepatoma derived growth factor (HDGF)
• Insulin-like growth factor (IGF)
• Myostatin (GDF-8)
• Nerve growth factor (NGF) and other neurotrophins
• Platelet-derived growth factor (PDGF)
• Thrombopoietin (TPO)
• Transforming growth factor alpha (TGF-α)
• Transforming growth factor beta (TGF-β)
• Vascular endothelial growth factor (VEGF)

Cancer cells use many growth factors to their advantage.

In addition to circulating GF’s, many GF’s are made within the tumor niche, by the cancer cells themselves or by neighboring stroma or immune cells.

Endocrine/
Autocrine/Paracrine
Insulin Like Growth Factor 1 and 2
IGF-1, IGF-2

IGF-1 is normally produced by the liver and stimulated by Growth Hormone (GH).

Estrogen Receptor alpha (ERα) can translocate to the cell membrane and bind/stimulate IGFR1. (Not so for ERβ)
Circulating IGF-1 levels


- IGF-1 mRNA in the liver was positively associated with dietary casein (rats) – British Journal of Nutrition 67 (2): 257.
C-peptide/Insulin

C-peptide is concordant with insulin levels, with less variability

- Insulin promotes Tamoxifen resistance (via transcription factor T-bet)
- Insulin is known to decrease binding proteins (BP’s) for IGF-1, rendering more IGF-1 available
- C-peptide is inversely assoc. with SHBG (thus increasing free estrogens)
- Higher serum levels of C-peptide assoc. with sig lower EFS(1)

(1) *Journal of Clinical Oncology*, 2006 ASCO Annual Meeting Proceedings
Vol 24, No 18S (June 20 Supplement), 2006: 524
• Diet
• Exercise
• Avoidance of exogenous IGF-1 or GH
• Caution with some “anti-aging” protocols that raise GH
IGF-I and Natural Agents that block downstream signals of growth, survival and metastasis
Natural agents that block/ lower IGF-1

- green tea polyphenol (GTP in pathway)
- lycopene
- curcumin
- silibinin
- apigenin
- resveratrol
- genistein
- Retinoic acid increases BP-3 (the predominant BP)
- $1,25(OH)_2D_3$ increases BP-3
- Melatonin
Estrogens and their metabolites

- Goal: Increase 2 and decrease 16 metabolites
- Avoid exogenous Est’s
- Fish oil
- Flax seeds
- I3C/ DIM
- Isoflavones (?)
- Weight loss
- Exercise
- Rosemary
- Turmeric
<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Cellular responses</th>
<th>Signaling targets</th>
<th>Ref.</th>
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</thead>
<tbody>
<tr>
<td>DIM</td>
<td>1. Apoptosis induction and cell cycle arrest</td>
<td>Akt phosphorylation</td>
<td>[14,38-46,50,51]</td>
</tr>
<tr>
<td></td>
<td>2. Inhibition of angiogenesis</td>
<td>NF-κB signaling</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Androgen receptor (AR) down-regulation</td>
<td>Survivin expression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Activation of aryl hydrocarbon receptor (AhR) and consequent activation gene expression of Phase I and II enzymes</td>
<td>Bcl-2 expression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Inhibition of ERα-dependent gene expression</td>
<td>Cdc25A expression</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>CDK 6 expression</td>
<td></td>
</tr>
<tr>
<td>ICZ</td>
<td>Activation of AhR and consequent activation of gene expression of Phase I and II enzymes</td>
<td>AhR signaling</td>
<td>[47,48]</td>
</tr>
<tr>
<td>LTr₁</td>
<td>1. An antagonist of estrogen receptor (ER)α</td>
<td>ER signaling</td>
<td>[52]</td>
</tr>
<tr>
<td></td>
<td>2. A weak agonist of AhR</td>
<td>AhR signaling</td>
<td></td>
</tr>
<tr>
<td>CTr</td>
<td>A potent agonist of (ER)α</td>
<td>ER signaling</td>
<td>[53]</td>
</tr>
<tr>
<td>CTet</td>
<td>Cell cycle arrest</td>
<td>CDK 6 expression</td>
<td>[49]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p27kip1 expression</td>
<td></td>
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</tbody>
</table>

↓, down-regulation; ↑, up-regulation.
Estrogenomics-

• Tests for the presence of SNP’s in metabolic pathways of estrogen metabolism
• Inflammatory markers
• Vitamin D receptor
• Coagulation
Estrogenomics

Estrogen Metabolism
- CYP1A1 • CYP1B1
- GST (M1 and P1)
- COMT (catechol-O-methyl transferase)

HyperCoagulation
- GP3a (Glycoprotein 3)
- PAI-1 (Plasminogen activator inhibitor-1)
- Factor 2 (Prothrombin)
- Factor 5 (Leiden)

Cardiovascular
- Apo E (Apolipoprotein E)
- MTHFR
- TNF-α • IL-6

Osteoporosis
- VDR • COL1A1
- TNF-α • IL-6
SNPs and Tamoxifen metabolism

Women with SNP in CYP2D6 who are poor metabolizers do not benefit from Tamoxifen and have a 3.8x increased risk of recurrence.


Gratitude to Lise Alschuler, ND, FABNO for this slide.
Should we test estrogens? Metabolites? SNP’s?

• Serum Estradiol, SHBG, testosterone
  – Salivary testing?

• 2/16 metabolite testing
  – Yes: in patients not taking aromatase inhibitors
  – Measure baseline when patient is living a lifestyle they can permanently maintain

• Estrogenomics
Vascular Endothelial Growth Factor

<table>
<thead>
<tr>
<th>Function</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>Proliferation</td>
<td>Activation of mitogen-activated protein kinases</td>
</tr>
<tr>
<td>Permeability</td>
<td>Vesicovascular organelles, Endothelial fenestrations, Opening of junctions between adjacent endothelial cells</td>
</tr>
<tr>
<td>Invasion</td>
<td>Induction of metalloproteinases uPA, uPAR, TTPA</td>
</tr>
<tr>
<td>Migration</td>
<td>Activation of FAK, p38, nitric oxide</td>
</tr>
<tr>
<td>Survival</td>
<td>Induction of PI3K/Akt, Bcl2, A1, survivin, XIAP, or FAK Inhibition of caspases</td>
</tr>
<tr>
<td>Activation</td>
<td>Upregulation of integrin expression, Alteration of cell cytoskeleton</td>
</tr>
</tbody>
</table>

Vascular Endothelial Growth Factor

- VEGF is expressed in the majority of invasive ductal carcinoma’s, regardless of stage/grade/histology
- VEGF expression in tumor tissue is strongly associated with high microvascular density (poorer prognosis)
- Over-expression of VEGF in cancer cells correlates with poor prognosis in breast cancer
- 50,000 x more powerful than histamine at increasing capillary permeability
Fibrinogen/ fibrin and angiogenesis


• Ultimately, lowering VEGF is goal

• Lower Fibrinogen with:
  - Curcumin
  - Garlic
VEGF- expressed throughout growth
Circulating VEGF and IL-6

• No significant difference in levels of serum VEGF or platelet derived VEGF, in normal (n=26) vs. local (n=31) vs. metastatic (n=73) breast cancers.

• Serum levels of IL-6 were 10 times higher in women with distant metastasis compared to locoregional disease.
  – (Clin Breast Cancer. 2002 Jan;2(4):311-5. Serum interleukin 6, EGF, serum VEGF, and VEGF platelet load in breast cancer patients)
Interleukin-6

• Serum and plasma concentrations of VEGF and serum concentration of IL-6 were measured in 87 patients with a fully documented history of hormone-refractory metastatic breast cancer...

• The presence of high levels of serum IL-6, but not VEGF, was significantly correlated with shorter survival.

VEGF levels not correlated to survival

- Plasma or serum VEGF not correlated with survival in metastatic breast cancer patients

However, where there’s VEGF, there’s IL-6...
Interleukin-6

Figure 2  Survival of patients as a function of serum IL-6 levels. Patients with high levels of serum IL-6 constituted a subgroup of very poor prognosis. The cutoff value (55 pg ml$^{-1}$) represents the highest quartile for serum IL-6 levels when detectable.

IL-6

- IL-6 expression of tumors of women with early stage carcinomas correlated with low grade, ER+ status and better prognosis
- IL-6 upregulates aromatase in malignant tissue
- Inhibits apoptosis
- Promotes osteoclast formation and inhibits dendritic cell differentiation
Should we test IL-6?

• As with all testing that renders prognostic information, the clinical benefit is weighed against the possible psychological risk.
Natural Agents that inhibit VEGF

- Alliin
- Caffeic acid
- Capsaicin
- Curcumin
- Diallyl disulfide, diallyl sulfide
- Gingerol, perillyl alcohol (D-limonene)
- Phytic acid
- rosmarinic acid
- sulforaphane
Herbs that decrease VEGF

Artemisia annua (Chinese wormwood)
Viscum album (European mistletoe)
Curcuma longa (turmeric)
Camellia sinensis (green tea)
Vitis vinifera (grape seed extract)
Angelica sinensis (dong quai)
Taxus brevifolia (Pacific yew)
Scutellaria baicalensis (Chinese skullcap)
Polygonum cuspidatum (Japanese knotweed)
Silybum marianum (milk thistle)
Magnolia seed cones
Other Chinese herbs (see Table vi)

Sagar et al. Curr Oncology, 2006;13(1)
Natural Agents that inhibit IL-6

• Resveratrol—300-500 mg transresveratrol qd
• Green Tea--
• Luteolin—celery, parsley, tomatoes,
• Apigenin- food derived
• Curcumin--

• Shifting to immune balance from Th2 to Th1
  – Trametes
  – Ganoderma
  – Agaricus
Think NF KappaB and Cox-2 inhibitors to dampen many of the proliferative, angiogenic, metastatic and cachexic pathways all at once.
C Reactive Protein

• “CRP may be important prognostic markers for long-term survival in breast cancer patients, independent of race, tumor stage, and body mass index.”
  – Higher CRP correlated with reduced DFS

• CRP measured in Br Ca patients (NED) at 31 months
  – Positively correlated with BMI, smoking, waist circumference, age, less physical activity
  – Negatively correlated with Vitamin E and Tamoxifen use
Above image from: Cancer is a Preventable Disease that Requires Major Lifestyle Changes. *Pharmaceutical Research* **Volume 25, Number 9 / September, 2008**
Sleep Deprivation and Activation of Morning Levels of Cellular and Genomic Markers of Inflammation

Michael R. Irwin, MD; Minge Wang, MSN; Capella O. Camponayor, MS; Alicia Collado-Hidalgo, PhD; Steve Cole, PhD

Background: Inflammation is associated with increased risk of cardiovascular disorders, arthritis, diabetes mellitus, and mortality. The effects of sleep loss on the cellular and genomic mechanisms that contribute to inflammatory cytokine activity are not known.

Methods: In 30 healthy adults, monocyte intracellular proinflammatory cytokine production was repeatedly assessed during the day across 3 baseline periods and after partial sleep deprivation (awake from 11 PM to 3 AM). We analyzed the impact of sleep loss on transcription of proinflammatory cytokine genes and used DNA microarray analyses to characterize candidate transcription-control pathways that might mediate the effects of sleep loss on leukocyte gene expression.

Results: In the morning after a night of sleep loss, monocyte production of interleukin 6 and tumor necrosis factor α was significantly greater compared with morning levels following uninterrupted sleep. In addition, sleep loss induced a more than 3-fold increase in transcription of interleukin 6 messenger RNA and a 2-fold increase in tumor necrosis factor α messenger RNA. Bioinformatics analyses suggested that the inflammatory response was mediated by the nuclear factor κB inflammatory signaling system as well as through classic hormone and growth factor response pathways.

Conclusions: Sleep loss induces a functional alteration of the monocyte proinflammatory cytokine response. A modest amount of sleep loss also alters molecular processes that drive cellular immune activation and induce inflammatory cytokines; mapping the dynamics of sleep loss on molecular signaling pathways has implications for understanding the role of sleep in altering immune cell physiologic characteristics. Interventions that target sleep might constitute new strategies to constrain inflammation with effects on inflammatory disease risk.

Arch Intern Med. 2006;166:1756-1762
Extended treatment with physiologic concentrations of dietary phytochemicals results in altered gene expression, reduced growth, and apoptosis of cancer cells

Elena P. Moiseeva,1 Gabriela M. Almeida,2 George D.D. Jones,2 and Margaret M. Manson1
1Cancer Biomarkers and Prevention Group and 2Radiation and Oxidative Stress Group, Department of Cancer Studies, University of Leicester, Leicester, United Kingdom

Abstract
Dietary phytochemicals exhibit chemopreventive potential in vivo through persistent low-dose exposures, whereas mechanistic in vitro studies with these agents generally use a high-dose single treatment. Because the latter approach is not representative of an in vivo steady state, we investigated antitumor activity of curcumin, 3,3-dimethoxybenzene (DIM), epigallocatechin gallate (EGCG), genistein, or indole-3-carbinol (I3C) in breast cancer MDA-MB-231 cells, exposed in long-term culture to low concentrations, achievable in vivo. Curcumin and EGCG increased cell doubling time. Curcumin, EGCG, and I3C inhibited clonogenic growth by 55% to 60% and induced 1.5- to 2-fold higher levels of the basal caspase-3/7 activity. No changes in expression of cell cycle–related proteins or survivin were found; however, I3C reduced epidermal growth factor receptor expression, contributing to apoptosis. Because some phytochemicals are shown to inhibit DNA and histone modification, modulation of expression by the agents in a set of genes (cadherin-11, p21Cip1, urokinase-type plasminogen activator, and interleukin-6) was compared with changes induced by inhibitors of DNA methylation or histone deacetylation. The phytochemicals modified protein and/or RNA expression of these genes, with EGCG eliciting the least and DIM the most changes in gene expression. DIM and curcumin decreased cadherin-11 and increased urokinase-type plasminogen activator levels correlated with increased cell motility. Curcumin, DIM, EGCG, and genistein reduced cell sensitivity to radiation-induced DNA damage without affecting DNA repair. This model has revealed that apoptosis and not arrest may be responsible for growth inhibition. It also implicated new molecular targets and activities of the agents under conditions relevant to human exposure. [Mol Cancer Ther 2007;6(11):3071–9]

Introduction
Epidemiologic studies indicate that consumption of vegetables, containing dietary phytochemicals, reduces cancer risk (1). Many dietary phytochemicals not only block development of tumors but also inhibit metastatic growth in animal models (Supplementary Table S1). Potential use of dietary agents in combination therapies has been considered among novel treatment approaches because combining phytochemicals with radiotherapy and chemotherapy improves outcome in animal models (Supplementary Table S1).

The majority of studies on these agents in cell culture use short exposure times to high concentrations, often orders of magnitude greater than those achievable in vivo. Moreover, treatment with a single dose provides data on an acute induction response, whereas in vivo anticancer activity arises from a steady-state response to the continued presence of dietary agents. Therefore, many reported effects obtained in cell culture studies may be irrelevant for in vivo activity. All the chemopreventive phytochemicals induce cell cycle arrest and cell death, albeit at different levels of investigation (e.g., growth, apoptosis, and expression of selected biomarkers) could be detected following extended treatments.
P53 tumor suppressor

DNA damage
Chemical carcinogens
UV, γ, and X irradiation

↓

p53

↓

p21

DNA repair
Cell cycle arrest
Apoptosis

↓

Maintenance of genomic integrity
Serum anti-p53 antibodies are correlated with decreased survival in cancer patients. Muller. Int J Oncology 2006

Could p53 be used to help determine therapy?:
206 node neg patients.
31 pts had mutant p53 (tumor tissue) Radiation tx sig increased EFS in pts with mutant p53 but not wild type

Inducers of Apoptosis indepent of p53:
Vitamin D (1,25) Vitamin E, Genestein
Apoptotic agents

- Flavonoids: luteolin, genistein, naringenin, apigenin and diazein
- Garlic
- Resveratrol
- Curcumin
Homocysteine

Silencing of CpG Regions

- Inactivation of tumor suppressor genes such as p53
- Inactivation of DNA repair genes

Hypo/hypermethylation

- Some SNP’s in MTHFR gene confer greater risk for several cancers:
  - Including breast
- Hypomethylation by a group of demethylases
- Hypermethylation through DNA methyltransferase
  - Green tea inhibits this enzyme
The CoRN Reports...

- CoRN = CoQ10 (100mg), Riboflavin (10mg), Niacin (50mg)

- Reduced CEA and 15-3
- Decrease in serum IL-1beta, IL-6, IL-8, TNF-alpha and VEGF
- Counteracts TAM induced hyperlipidemia
- Increased antioxidant status while decreasing lipid peroxide levels
Tests to do with your patients

- Vitamin D (25-dihydroxycholecalciferol)
- C-Reactive Protein
- Hemoglobin A1C, C-peptide, insulin
- 2/16 hydroxyestrone metabolites
- Homocysteine
- Estrogenomics (?)
- IgG food allergies (will affect inflammation...)
- IL-6(?) or VEGF?— more well established for patients with stage III or IV
The future?

- Proteomics looks at protein patterns in the blood. Patterns unique to certain diseases emerge and may predict the presence of disease long before imaging.
On the fringe...

• Worthy of noting for their potential, but clinical utility not yet known:
• All tests mentioned, but not yet recommended by ASCO (earlier slide)
• Mammoglobin= unique protein + in 72% of br ca pts
• Autoantibodies to c-myc, p53, MUC1 (1/8/2010; http://etheses.nottingham.ac.uk/876/)
Websites for more info

• VEGF: Researchvegf.com
• Oncotypedx.com– click on “clinical summary”
• Oncologystat.com
• Medscape
• Cellsignalling.com-- pathways