

STRATEGIC PLANNING FOR RISK REDUCTION: HOW TO REDUCE CANCER RISK



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Nutrition Assessmental Lab

- B12, folate, mercury, copper, lead levels
- Thyroid function
- Cardio C reactive protein, ESR
- Serum 25-OH Vitamin D
 - . CoQ 10 levels
- Fasting glucose, insulin, Hemoglobin A1C
- Cellac Panel
- Natural Killer cells

Cancer, Diet , Causes


Inflammation/Mediators

Oxidative Overload

Glycemic Overload

Detoxification

Cancer and Environment




- One in 3 Americans will hear the words "You have cancer"
- More Americans are surviving cancer – 9.8 million Americans in 2001 vs 3 million living with cancer in the early 1970s
- Cancer rates are increasing in many categories:
 - In 2003 cancer cases in US increased 3.8%
 - Non-Hodgkin Lymphoma rates tripled since 1950's
 - 1 in 7 women develop breast cancer.

EPIC : DIET AND CANCER May,2004

- The European Prospective Investigation into Cancer and Nutrition (EPIC) :The study registered 519, 978 participants between 1992 and 2000 in 10 European countries. Cancer incidence and cause-specific mortality to be f/u for several decades.
- **"Diet is the second leading cause (25%) of all cancers"**


NEJM Twin Study



- Identical twins developed same disease only 10% of the time
- Both develop either breast, colon or prostate cancer 14 – 30% of the time

New England Journal of Medicine, 2000

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K-ras, Oncotype DX, CYP2D6

By increasing efficacy and screening out patients who likely will not respond to a particular drug, biomarkers improve patient care and the treatment of cancer, while reducing costs associated with unnecessary less effective therapies.

CRUCIFEROUS VEGETABLES:

- 1- Cruciferous vegetables (e.g. broccoli, cabbage and Brussels sprouts) appear to protect against the development of cancer.
- 2- Indole derivatives including indole -3-carbinol induce levels of cyt P450 1A1 in the intestine
- 3- Induction of P4501A1 occurs at a transcriptional level

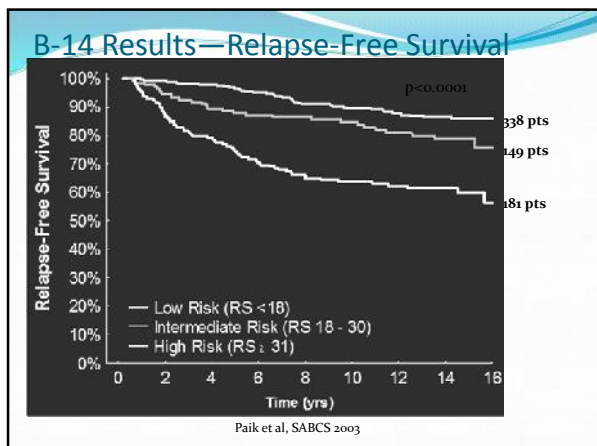


GAYNOR INTEGRATIVE ONCOLOGY: Treatment + Healing=Care

- Patients given cancer therapeutic options as well as late effects of cancer treatments, with expected time course
- Comprehensive plan for healthy lifestyle to prevent recurrence and reduce the risk of other comorbid conditions. Includes nutrition, exercise and psychospiritual support
- Gaynor Wellness (gaynorwellness.com) Cancer prevention strategies

OncotypeDx Predictive Biomarker Therapeutically Relevant Gene Expression Signature

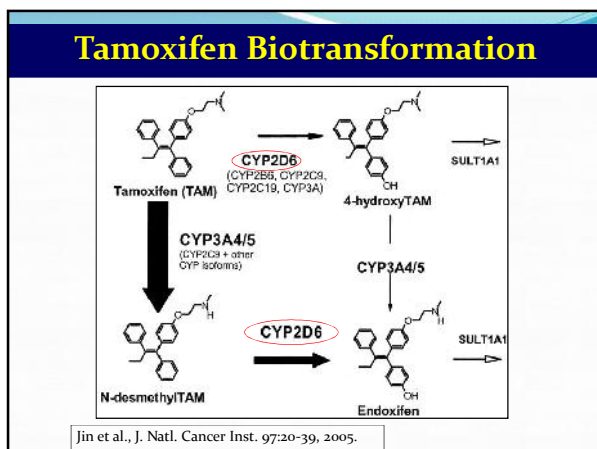
- <10% of node negative ER+ breast cancer patients require or benefit from the cytotoxic chemotherapy that they receive
- Identify patients with node negative ER+ breast cancer who have low risk of recurrence on tamoxifen alone



Fasting Insulin and Outcome in Early-Stage Breast Cancer: Results of a Prospective Cohort Study

Purpose: Insulin, a member of a family of growth factors that includes insulin-like growth factor (IGF)-I and IGF-II, exerts mitogenic effects on normal and malignant breast epithelial cells, acting via insulin and IGF-I receptors. Because of this and because of its recognized association with obesity, an adverse prognostic factor in breast cancer, we examined the prognostic associations of insulin in early-stage breast cancer.

J Clin Oncol 20(1):42-51, January 1, 2002



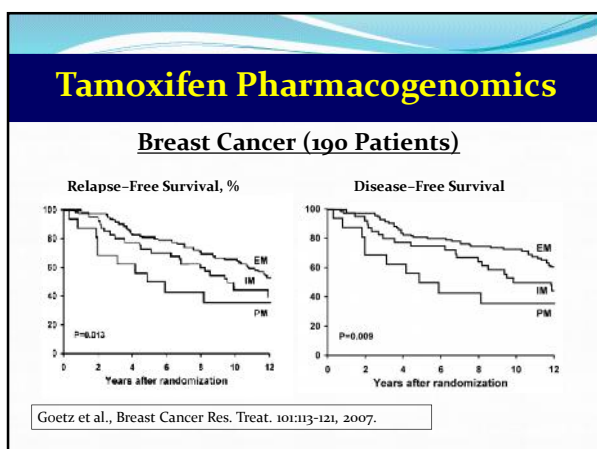
IGF-1 as Biomarker

- Similar in structure to insulin
- Regulated by growth hormone
- Levels of growth hormone and IGF-1 decline as men and women age
- This decrease is believed to be linked to health problems associated with old age

Study:

- 633 men, aged 50 and older.
- IGF-1 levels were measured between 1988 and 1991
- 18 years of follow-up, men whose IGF-1 levels were above 100 nanograms per milliliter at the start of the study twice as likely to die of cancer as those with lower levels
- The increased risk of cancer death for older men with high levels of IGF-1 was not explained by differences in age, body size, lifestyle or cancer history.

March 2010, Journal of Clinical Endocrinology & Metabolism



Insulin Resistance Biomarkers

Insulin resistance syndrome:

- * high triglycerides
- * low HDL
- * high circulating insulin levels
- * linked to diabetes, increased cancer incidence, and heart disease

METFORMIN

- From diabetes to cancer... via angioprevention?
- It received approval by the U.S. Food and Drug Administration (FDA) for Type 2 diabetes in 1994. Metformin is an insulin-sensitizer that reduces blood sugar levels: it reduces hepatic glucose output and increases peripheral glucose metabolism
- **Cardiovascular benefit (UKPDS and PRESTO study)**

VITAMIN D AND BREAST CANCER

- Garland, Cedric et al. (UCSD) AACR 2006
Meta-analysis 1,760 women- 25-OH Vit. D levels
Multiple regression analysis: D₃ level >52ng/ml assoc with 50% lower risk breast CA compared with levels <12 ng/ml.
- Previous study (Prev Med 1990;19:614-22):
Demonstrated women living closer to the equator, had significantly lower risk of breast cancer death

- From diabetes to cancer... via angioprevention
- **Epidemiological studies have confirmed that metformin, but not other anti-diabetic drugs, significantly reduces cancer incidence and improves cancer patients' survival in type 2 diabetics.**
 - Evans JM et al. BMJ 2005
 - Landman GW et al. Diabetes Care 2010
- **A decreased risk of breast cancer was observed in female patients with type 2 diabetes using metformin on a long term basis.**
 - Bodmer M et al. Diabetes Care 2010

VITAMIN D DEFICIENCY LINKED TO POORER OUTCOME IN BREAST CANCER

- Women who had very low 25-OH vitamin D levels were 94% more likely to develop metastases (69% vs. 83% DFS) and 73% more likely to die (74% vs. 85% OS at 11.6 yrs) than women with normal levels at time of diagnosis.
- 37.5% had deficient levels below 50
- 24% had "sufficient" levels over 72
- {ASCO 2008 Annual Meeting}

Mature Analysis from Women's Intervention Study (WINS)

- Chlebowski, RT et al. SABCS 2006 Gen. Session 5: Abst 32 and JNCI Dec 2006
- 2400 women with early breast cancer at UCLA: randomized prospective trial--low fat (less than 20% cal. from fat) vs. control
- At 5.8 yrs; 22% fewer deaths- low fat diet
- Those with ER-/PR- there was a 66% reduction in mortality


Biomarkers

- **Infectious Agents (HPV, H.pylori, D-arabinitol for yeast overgrowth)**
- **Inflammation (CRP, ESR, fatty acid metabolism)**
- **Metabolic syndrome (IGF-1, A1C, beta-hydroxybutyrate, insulin)**
- **Hormones**
- **Immunologic (NK cell number/activity)**
- **Inherited Susceptibility Polymorphisms, BRCA**
- **Micronutrients (selenium, zinc)**

Inherited Breast / Ovarian Cancer

BRCA1 or 2 Mutation
Future of Predictive Genomics

- Women have an 82% lifetime risk of breast or ovarian cancer
- Risk has increased since 1940
 - Risk of breast cancer 24% if born before 1940 but 67% if born after 1940
 - Risk of ovarian cancer was twice as high for BRCA1 carriers and 23% higher for BRCA2 carriers if born after 1940



King et al. Science 24 October 2003 Vol. 302 P 643-646

Epidemiological link

Communities with highest dietary isoflavone levels have the lowest incidences of breast cancer

Soy and Breast Cancer

Soy Food Intake and Breast Cancer Survival Xiao Ou Shu, MD, PhD; Ying Zheng, MD, MSc; Hui Cai, MD, PhD; Kai Gu, MD; Zhi Chen, MD, PhD; Wei Zheng, MD, PhD; Wei Lu, MD, PhD

- *JAMA*. 2009;302(22):2437-2443.
- **Context** Soy foods are rich in isoflavones, a major group of phytoestrogens that have been hypothesized to reduce the risk of breast cancer. However, the estrogen-like effect of isoflavones and the potential interaction between isoflavones and tamoxifen have led to concern about soy food consumption among breast cancer patients.
- **Objective** To evaluate the association of soy food intake after diagnosis of breast cancer with total mortality and cancer recurrence.
- **Design, Setting, and Participants** The Shanghai Breast Cancer Survival Study, a large, population-based cohort study of 5942 female breast cancer survivors in China. Women aged 20 to 75 years with diagnoses between March 2000 and April 2006 were recruited and followed up through June 2009. Information on cancer diagnosis and treatment, lifestyle exposures after cancer diagnosis, and disease progression was collected at approximately 6 months after cancer diagnosis and was reassessed at 3 follow-up interviews conducted at 0, 36, and 60 months after diagnosis. Annual record linkage with the Shanghai Vital Statistics Registry database was carried out to obtain survival information for participants who were lost to follow-up. Medical charts were reviewed to verify disease and treatment information.
- **Results** During the median follow-up of 3.9 years (range, 0.5-6.2 years), 444 deaths and 134 recurrences or breast cancer-related deaths were documented in 5913 surgically treated breast cancer patients. Soy food intake, as measured by either soy protein or soy isoflavone intake, was inversely associated with mortality and recurrence. The hazard ratio associated with the highest quartile of soy protein intake was 0.76 (95% confidence interval [CI], 0.64-0.92) for total mortality and 0.68 (95% CI, 0.49-0.97) for recurrence compared with the lowest quartile of intake. The multivariate-adjusted 4-year mortality rates were 8.3% and 7.4%, and the 4-year recurrence rates were 11.2% and 8.0%, respectively, for women in the lowest and highest quartile of soy protein intake. The inverse association was evident among women with either estrogen receptor-positive or -negative breast cancer and was present in both users and nonusers of tamoxifen.
- **Conclusion** Among women with breast cancer, soy food consumption was significantly associated with decreased risk of death and recurrence

Soy Isoflavones and Breast Proliferation

Palomares, M. San Antonio Breast Cancer Symposium (2005) (Poster)

- 23 postmenopausal breast cancer (Stage I, II, DCIS) patients at City of Hope National Medical Center
- Randomized: Isoflavone tab 100mg/d vs. placebo for 1 year
- Bx contralat. breast at 0, 6, and 12 mo: Ki67 index decreased from baseline in Rx group by 3.1% vs 0.9% control (6 mo.) and 4.9% vs 4.1% (12 mo.) "Our findings suggest no negative effects of soy and perhaps even a beneficial effect."

How estrogenic are phenolic phytoestrogens?

17 β -estradiol	1
Coumestans	50 (=Estradiol)
Isoflavones	1000
Flavones/ Flavonols/	5000
Flavanones	.
Lignans	5000
Chalcones	5000

Phara G, Hu, Ferasidha G, H. Naturally Occurring phytoestrogens in foods - A review Food Additives and Contaminants (1999) 2, 73-106

Nurses Health Study

- Women who take Aspirin regularly following a breast cancer diagnosis cut their risk of death and metastasis by nearly 50%.
- "aspirin has relatively benign adverse effects compared with cancer chemotherapeutic drugs and may also prevent colon cancer, cardiovascular disease, and stroke"
- Appears to affect estrogen receptor-positive and -negative tumors.
- (J. Clin. Oncol. October 2010)


SOY ISOFLAVONES AND BREAST PROLIFERATION

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BREAST MILK CONTAMINANTS WHICH ARE ENDOCRINE DISRUPTORS

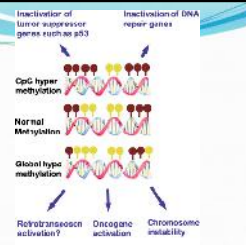
*heptachlor	*dioxin
*chlordane	*benzene
*endrin	*toluene
*aldrin	*chloroform
*dieldrin	*styrene

- Aronson, KJ, et al, Queen University, Ontario
 "Breast adipose tissue concentrations of PCB's and other organochlorines and breast cancer risk"
Cancer Epidem. Biomarkers and Prev, Jan.2000.



Are we born with our genetic destiny or can it be changed?
 Agouti mice-- epigenetic changes carried across generations (Waterland and Jirtle, Mol Cell Biol. 23:5203-5210, 2003; Env Health Perspect 2006 April, 114(4) 567-572)

Nutritional genomics vs. toxicogenomics



Epigenetic markers: Markers for DNA methylation and histone modification

Omega-3 Fatty Acids

Breast cancer patients with higher fat tissue levels of DHA had improved response rates to chemotherapy that those with low levels.

(Bougnoux, P, et al. Cytotoxic drugs efficacy correlates with adipose tissue DHA level in locally advanced breast cancer. Br J Cancer 1999 Apr; 79(11-12): 1765-9

Omega-3-fatty acids have been found to:

- Increase chemo drug accumulation within cancer cells
- Reduce cancer cells proliferation by inhibiting protein kinase C activity

Diet May Influence Genetic & Epigenetic Events Associated with Several Cancer Processes

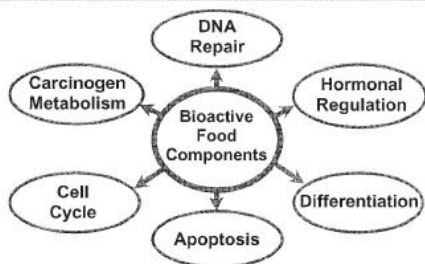


FIGURE 2 Bioactive food components are known to influence multiple biological processes. Determining which is most instrumental in bringing about a phenotypic change is critical to the future of nutrition and health because it will assist in determining who may benefit and who may be placed at risk by intervention strategies.

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Background and Significance

- Curcumin, the dietary pigment responsible for the yellow color of curry, is known to inhibit carcinogenesis in the skin, forestomach, duodenum and colon of experimental animals.
- Curcumin has been reported to have a variety of effects which could explain its chemopreventive properties. These include:
 - inhibition of arachidonic acid metabolism
 - inhibition of B[a]P-induced DNA adduct formation
 - inhibition of phorbol ester-induced tumor promotion
 - inhibition of activation of NF- κ B
 - suppression of AP-1-mediated transcription

ALPHA-LIPOIC ACID

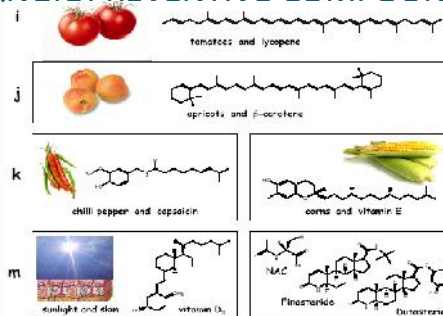
- Antioxidant that helps reduce free radicals
- Improves insulin sensitivity, reduces insulin resistance
- Appears to improve glucose transport
- Dosage: 200-800mg daily

Omega-3 Fatty Acids: EPA/DHA

- Essential fatty acids needed for healthy cells
- Improves cell function- lowers insulin resistance and improves metabolic balance
- Increases cell membrane fluidity, insulin binding to receptors, and insulin action
- 2-4 grams/day is recommended

(Lukaczer, Advance Nutr. Publication, 2001)

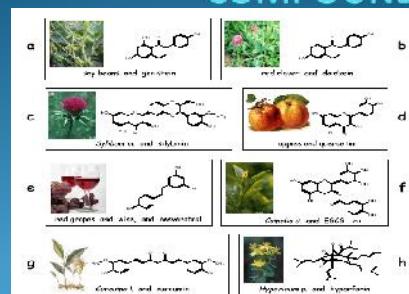
ANGIOPREVENTIVE COMPOUNDS



OBESITY VS. DETOXIFICATION

- Fat production or fatty acid synthesis depletes stores of NADPH, which is the body's ultimate reducing (antioxidant) agent.
- NADPH stores are required for the regeneration of antioxidants (ARE) and glutathione.

ANGIOPREVENTIVE COMPOUNDS



Araldi EM et al. *Curr Cancer Drug Targets.* 2008, 8(2):46-55

GREEN TEA

The most widely consumed herbal medicine in the world.

1. Growth-inhibiting effects of EGCG are specific against cancer cells.
2. EGCG is 20 times more potent an antioxidant than Vitamin E and 200 times more potent than Vitamin C.
3. EGCG is a DNA topoisomerase inhibitor against cancer cells (like doxorubicin) but without toxicity.
4. EGCG induces cancer cell apoptosis and inhibits activation of growth factor receptors and certain gene expression promoters essential for cancer division.

EXERCISE

- Aerobic exercise has been shown to reduce insulin resistance by improving blood supply to the muscle, which allows for more glucose uptake into muscle tissue.
- Exercise should be frequent and regular to be effective.
- Exercise should involve all the major muscle groups for at least 20-30 minutes 4-5 days/week.

GREEN TEA and ANGIOGENESIS

- EGCG inhibits angiogenesis by blocking the induction of vascular endothelial growth factor (VEGF) in human colon cancer cells.
- Physiologic concentrations (0.1 – 1 μ m) of EGCG induces potent inhibition of VEGF dependent tyrosine phosphorylation of VEGF receptor -2 (VEGF -2) which is similar to the pharmacologic agent Semaxanib.

Jung, Y.D., *Br J. Cancer* 2001; 84: 844-850
Lamy, S., *Cancer Res* 2002; 62: 381-385

VEGETERIAN PROTEIN SOURCES

Silken Tofu	3oz ¼ block	5 grams/protein
Block Tofu (in water)	3oz or 1/5 block	12 grams/protein
Tempeh	4oz (½ container)	12 grams/protein
Soy milk	8 ounces	10 grams/protein
Soy beans	½ cup	24 grams/protein
Legumes, beans, lentils	½ cup	6 grams/protein
Soy cheese	1 ounce	7 grams/protein
Nuts	¼ cup	5 grams/protein
Eggs	1	7 grams/protein
Yogurt	1cup	10-12 grams/protein
Cheese	1 ounce	7-10 grams/protein