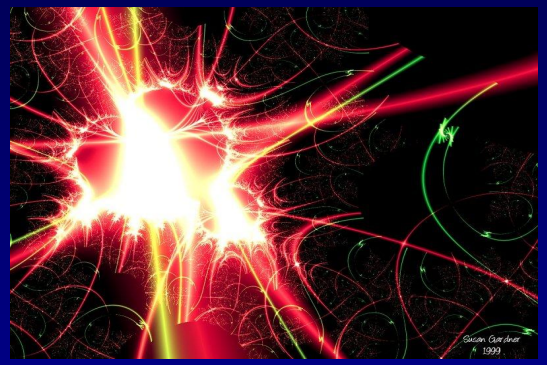
Antioxidants and Chemotherapy



Keith I. Block, M.D.

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Block Center for Integrative Cancer Care

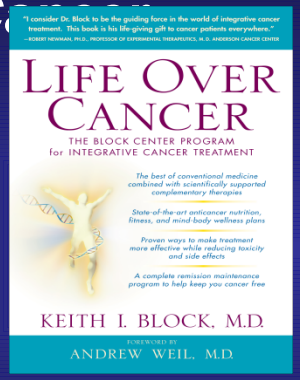
Director, Integrative Medical Education
University of Illinois College of Medicine

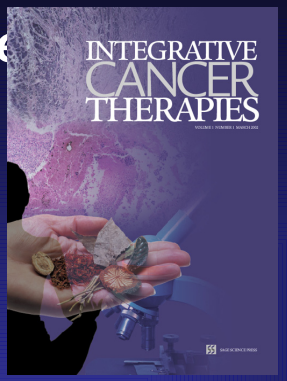
Editor-in-Chief of *Integrative Cancer Therapies*
Published by Sage Science Press

Member, Editorial Board Physician Data Query Cancer CAM
National Cancer Institute

DISCLOSURES

- Medical Director,
  Block Center for Integrative Cancer Treatment
- Editor-In-Chief,
  Integrative Cancer Therapie
- Author,
  Life Over C





Sage Publications
Peer-reviewed, Indexed Medline

www.ICT.Sage.com

www.BlockMD.com

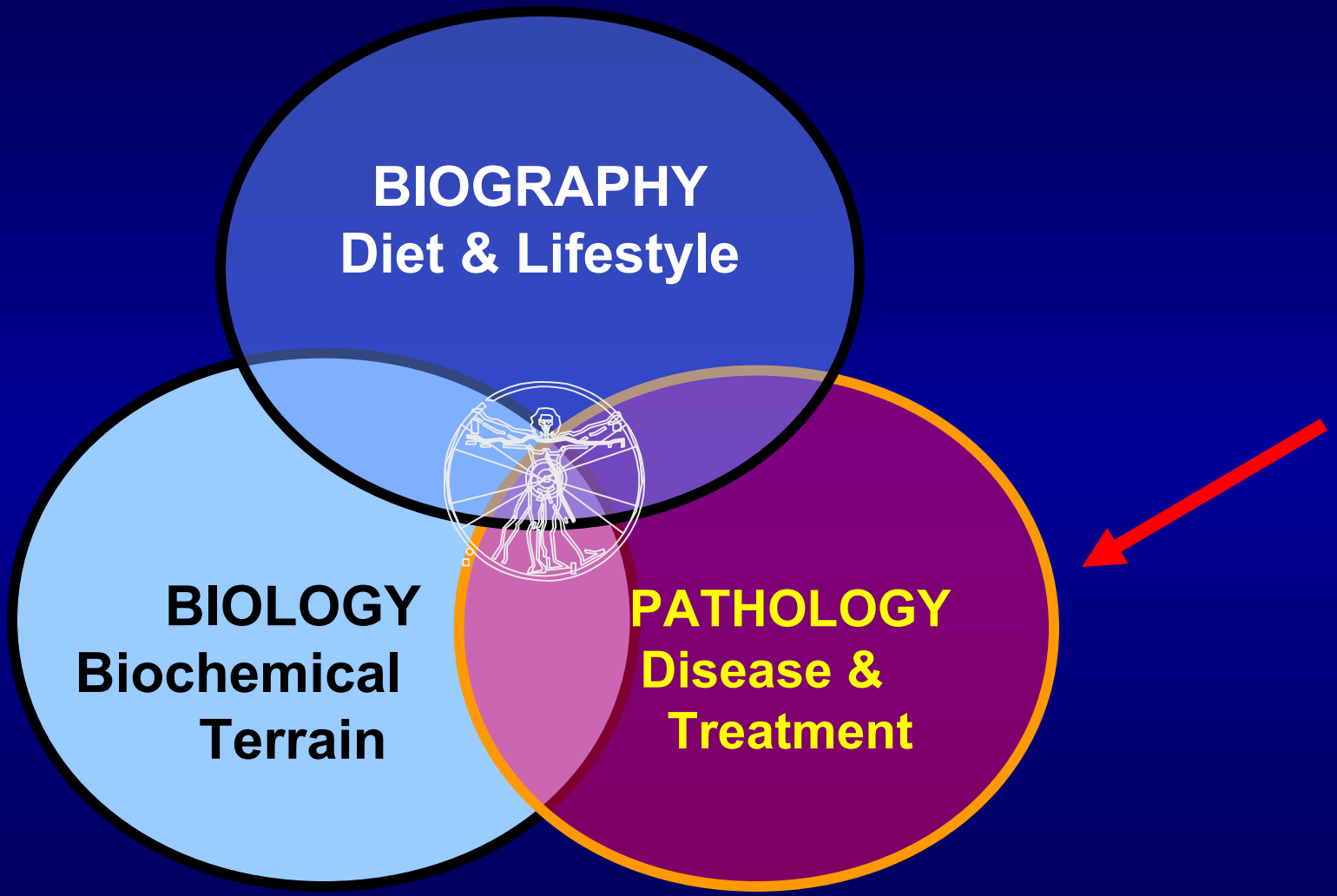
- Advisory Boards
  - American Botanical Council
  - Clarient / GE
  - Nerium Biotech
  - Atrium / Douglas Labs
  - Scientific Nutritional Formulator
  - Northshore Nutraceuticals

Block Center for Integrative Cancer Treatment

Opened Doors in *1980* – "ALL UNDER ONE ROOF"

- Physicians – (Medical Oncologists & Internists)
- Physician assistants
- Nurses (oncology-trained)
- Dietitians
- Physical therapist
- Physical care assistants - massage, chi gong, yoga
- Psychotherapists
- Ethnobotanist
- Research staff
- Hospital affiliations: SFH, Swedish Covenant
- Journal Editorial Staff: *Integrative Cancer Therapies*
- Research Projects: Univ of Illinois
- Resident & Student Rotations: UIC Medical; UIC Pharm College

The *LIFE OVER CANCER* Program for INTEGRATIVE CANCER TREATMENT



SYNERGISMS

OVERCOMING:
CANCER CHALLENGES

Life Over Cancer

BIOGRAPHY
Diet & Lifestyle

- Biobehavioral
- Physical
- Dietary

BIOLOGY
Terrain Factors
(Metabolic Hallmarks)

- Oxidative
- Inflammatory
- Growth Factor
- Immune**
- Coagulopathy
- Stress Chemistry

PATHOLOGY
& Treatment
(Molecular Hallmarks)

- Innovative Conv.
- Molecular **
- ChemoSens.Dx
- Chronomodulated

Experimentals
Immuno-therapies
Nutraceuticals
Off-Labels
OverSeas Rx

- Tumor Growth and Survival
- Rx Response/Outcome
- Rx Toxicity
- Life Quality
- Life-Threatening Complications
- Rx Life Journey

Individualized Regimens Based on Comprehensive Assessments & Monitoring

- Individualized Therapeutic Nutrition
- Personalized Fitness, Physical Therapy & Manual Treatment
- Tailored Mind-Spirit Strategies
- Circadian Health

- Biochemical Terrain – oxidation, inflammation, glycemia, …
- Molecular & Genomic Terrain – EGFR, Ras, BRAF, Cox-2, …
- Tailored Antioxidants & Nutraceuticals – Rx & Terrain Couplers

- Prescriptive Antioxidant Therapy
- Chronomodulated & Metronomic Chemotherapy
- IV C & Nutrient Infusions
- Chemo-sensitivity Testing
- Off-label Agents
- Over-seas Agents
- Vaccines – Immunotherapies
- Experimentals, Reasonable & Responsible Use of Alternatives


BLOCK CENTER

Definitions

- **Conventional –** Generally a single medical intervention model
- **Alternative -** In lieu of mainstream Rx, often, but not always, lacking rigorous evidence
-
- **Complementary medicine (CAM) -** Rx's are **single intervention add-ons** to mainstream medicine – ie. yoga or prayer or green tea or lycopene… (Most if not all institutional programs)
- **What's labeled "Integrative" -** "Selective **incorporation of elements** of CAM … **alongside solidly orthodox methods** of diagnosis and treatment." *(BMJ 2001; 322:119-20)*
- ***Life Over Cancer* - A systematic, comprehensive, multi-intervention, whole system model** with treatment strategies **individualized** to each patient based on **objective assessments** provided with a **life-affirming approach** and open communication between patients and practitioners.

Diet modification trials in breast cancer patients

Diet Intervention	Cancer	n	Design	Outcomes	Results	Reference
Low-fat diet – *fat intake <20%*	Breast, early stage, postmeno	2437	RCT	Relapse events, all: ER- subjects only: *~24% reduction in recurrence*	0.76 0.53	Chlebowski, 2006 (WINS)[1]
Low-fat, high fiber, fruit/vegetable	Breast, early	3088	RCT	Breast cancer event: Mortality:	0.96 0.91	Pierce, 2007 (WHEL)[2]
Support group, low-fat diet, exercise	Breast, regional	227	RCT	Recurrence: Cancer mortality: All-cause mortality:	0.55 0.44 0.51	Andersen, 2008[3]
Diet to support 10-kg weight loss	Breast, stage unclear	54	RCT	Cancer mortality: All-cause mortality:	0.38 .078	de Waard, 1993[4]
Diet to support 10-kg weight loss	Breast, stage unclear	48	RCT	Cancer mortality: All-cause mortality:	0.40 0.28	de Waard, 1993[4]
Lower kcal, low-fat diet	Breast, stage unclear	110	RCT	Recurrence:	0.20	Sopotsinskaya, 1992[5]

Results are hazard ratios; in all cases the cancer-related events occurred less frequently in the experimental diet group vs controls.

CUTTING DIETARY FAT ↓'s BREAST CANCER RECURRENCE

N=2,437 breast cancer patients s/p conv. Rx	Entire intervention Group	Risk of recurrence
Intervention 20% fat (33g)	24% reduction in risk of recurrence Statistically significant (p= .03)	
ER (-)		42% risk reduction (p=.02)
ER (+)		15% risk reduction (p=.28)
Control 30%+ (51g)	norm	norm

CONCLUSION: Reducing dietary fat intake significantly decreased risk of recurrence of postmenopausal breast cancer patients.

Chlebowski RT, Blackburn GL, et al. Phase III Women's Intervention Nutrition Study (WINS). 2005 ASCO Annual Meeting, Abstract #10. WINS STUDY

Flaxseed & Markers of Breast Tumor Growth

RCT, n=32 postmenopausal breast cancer patients.

Intervention: 25 g flaxseed muffin vs placebo muffin daily; eaten during period between biopsy & lumpectomy/mastectomy.

Results: pre-muffin vs post-muffin markers of tumor growth

Variable	Change Flax	Change Placebo	p
Ki-67 index	34.2% ↓	-	<.01
Apoptosis	30.7% ↑	-	<.01
HER-2	71% ↓	-	<.01

Conclusion:

Marked improvement in biomarker status in flax muffin group.

(Lignans in flaxseed -- <u>inhibit</u> Estrogen production.)

Thompson et al. 2005; Clin Cancer Res 11(10):3828-3835

A Healthy Diet is Core Foundation

1. RAINBOW OF VEGETABLES
2. WHOLE CEREAL GRAINS
3. Consume mostly PLANT-BASED PROTEINS, beans, soy, nuts, seeds and choose fish, omega-3 eggs & egg whites
4. FRUITS & BERRIES
5. LIMIT FAT INTAKE & choose HIGH QUALITY sources; deep-sea fish, seeds, nuts, avocados
6. Substitute *dairy alternatives* (soy, rice, almond) for milk products
7. Supplement with whole food-based GREEN DRINKS

Antioxidants are a valuable addition to a healthy diet !!!

Psycho-oncology intervention studies in cancer patients

Intervention	Cancer	n	Design	Outcomes	Results	Reference
Hypnosis, most pediatric	Various	6 RCTs	Meta-analysis	Chemotherapy n/v:	Large effect size	Richardson, 2007[1]
Progressive muscle relax-ation, imagery	Breast	60	RCT	Anxiety: Anticipatory n/v: Post-chemo n/v:	↓ ↓ ↓	Yoo, 2005[2]
Progressive muscle relaxation	Breast	71	RCT	n/v duration: n/v frequency: n/v intensity mood:	<.05 <.07 = <.05	Molassiotis, 2002[3]
Relaxation, imagery	Breast	80	RCT	Mature T-cells: Activated T-cells: LAK cells :	↑ ↑ ↑	Eremin, 2009[4]
Hypnosis, pre-biopsy	Breast	200	RCT	Propofol use : Pain : Nausea: Cost :	↓ ↓ ↓ ↓	Montgomery, 2007[5]
Psychological intervention	Breast	2207	RCT	*Recurrence : ↓45%* *Cancer mortality : ↓56%* *All-cause mortality:↓49%*	.55 .44 .51	Andersen, 2008[6]

Various outcomes; in almost all cases, subjects following the experimental intervention did significantly better compared to controls.

Outcome in Women with Breast Cancer

227 women Randomized to Psychological Intervention with 11 yr follow-up

Led to a *significant …*

Breast cancer recurrence	(HR of 0.55; P = .034)
Mortality from breast cancer	(HR of 0.44; P = .016)
Mortality from all causes	(HR of 0.51; P = .028)

Study suggests:

Integrative Mind-Spirit Interventions can favorably impact outcome!

Andersen, B. et al, *Cancer,* 2008
114 Intervention +

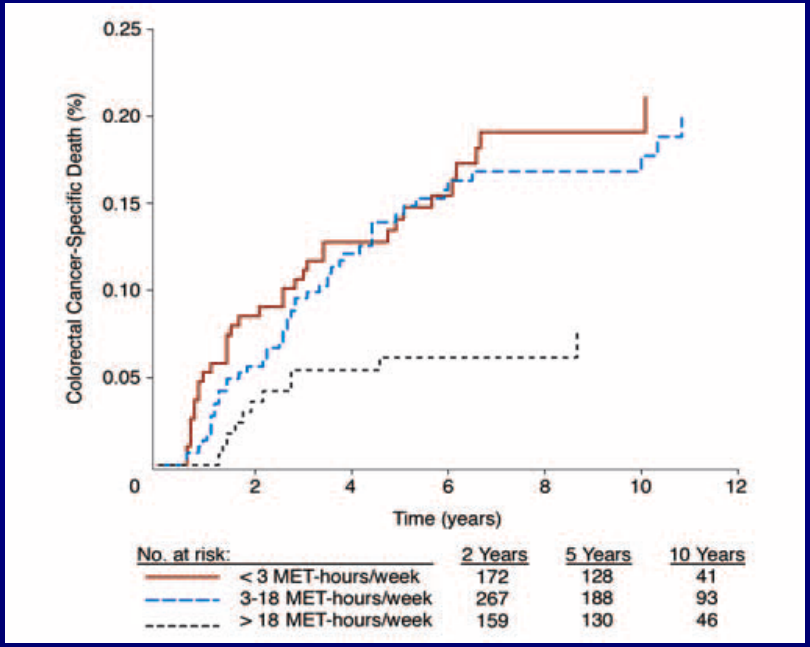
Exercise observational studies in cancer patients

Physical activity (PA) measurement	Cancer	n	Design	Outcomes	Results	Reference
PA, METs Shanghai	Breast, I-III	4826	Coh.	Total mortality: Cancer mortality	.70 .60	Chen, 2011[1]
Brisk vs slow walking	Prostate, localized	1455	Coh.	Progression:	.52	Richman, 2011[2]
Leisure time PA	Kidney	703	Survey	QOL, active vs sedentary:	8.6 points better	Trinh, 2011[3]
PA, METs, post-dx, WHI	breast	4643	Coh.	Cancer mortality: All-cause mortality:	.61 .54	Irwin, 2011[4]
PA, METs, at recurrence	breast	4482	Coh	Cancer mortality for 3-8 METs: 8-20 METs: > 20 METs:	 .65 .59 .51	Holick, 2008[5]
PA, METs, Nurses Health Study	Breast, I-III	2987	Coh.	Cancer mortality for 3-9 METs: 9-15 METs: 15-24 METs:	 .80 .50 .56	Holmes, 2005[6]
PA, METs, chemo patients *6-9 hrs aerobics*	Colon, III	832	Obs. in RCT	Disease-free surv. for 18-27 METs:, >27 METs: *Cut mortality and recur > 50%*	 .51 .55	Meyerhardt, 2006[7]

Results are hazard ratios or QOL surveys; in all cases subjects with higher exercise did better compared to least active subjects.

Physical Activity and Colon Cancer Survival

Observational cohort study, Stages I-III.
N=573 women, surveyed before diagnosis.



52 y/o Colon Cancer w/ Liver Mets

- 1997 - Recurrence, Liver mets, 5FU
- 2002 – Progressed, CPT-11
- Severe diarrhea, fatigue → hospice
- 2002 - Initial visit: BLOCK CENTER
  1st Rebuild: Full Integ Program
  2nd Rx: Chronomodulated CPT-11
- Complete Remission

Increasing physical activity by 6 hrs/wk → cut mortality by 61% ! (HR = 0.39)

6 - 9 hrs/wk of walking → Cut recurrence by ≥ half

Meyerhardt, J Clin Oncol. 2006 Aug 1;24(22):3535-41


OSTEOPOROSIS

"One-third of patients abandon chemotherapy prematurely due to physiological and psychological distress."

N = 472 women w/early-stage breast Ca.

- **Patients received 28% fewer treatment cycles than planned**
- **Cancer patients who didn't complete their full chemo cycles had shorter survival rates.**

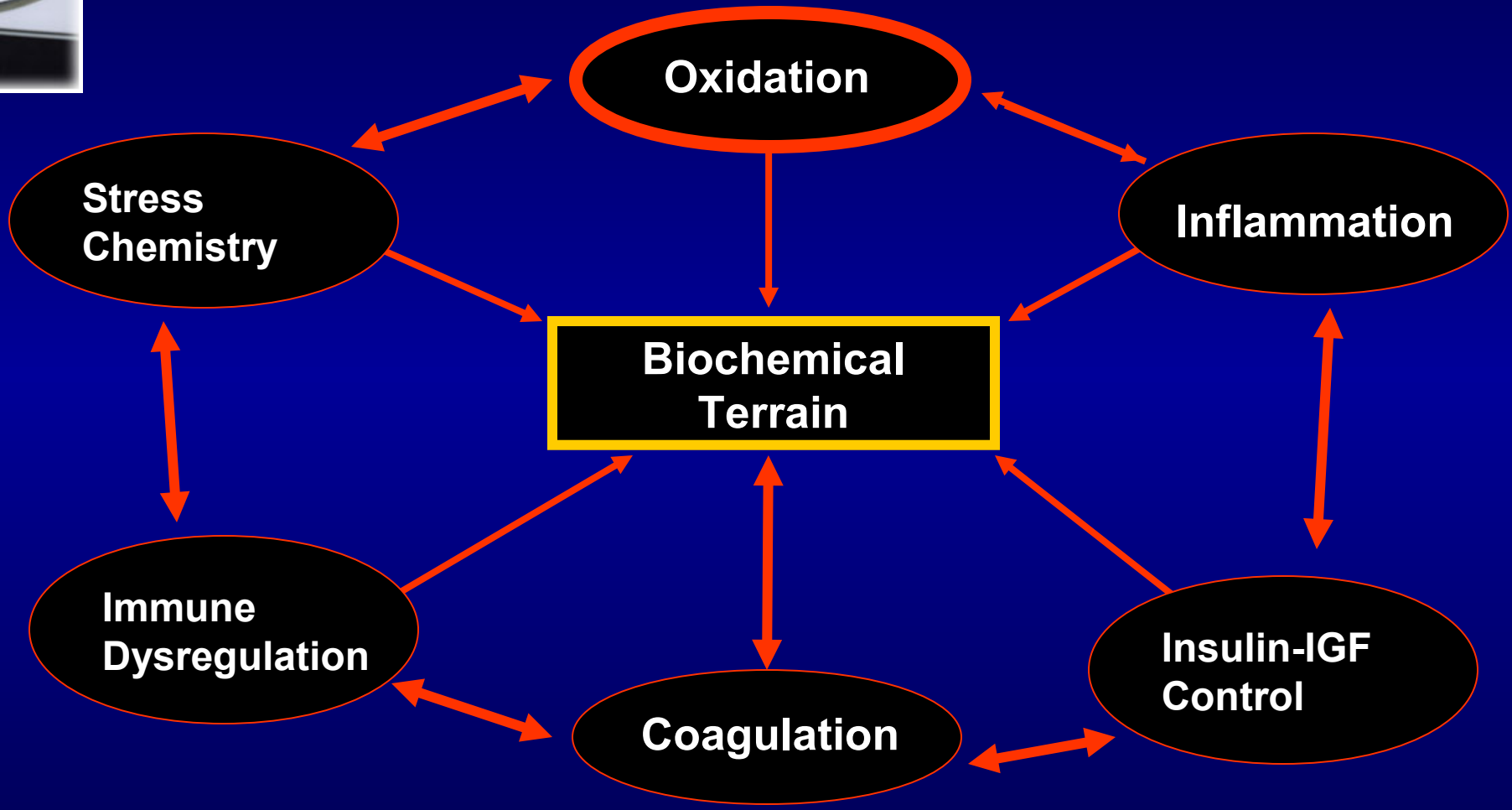
Integrative Rx, (e.g., antioxidants, etc.) → ⬇ toxicity, improve tolerance & QOL

→ ⬆ ability to complete chemoRx → improve survival.

(breast ca, colon ca, lung ca, … ….)

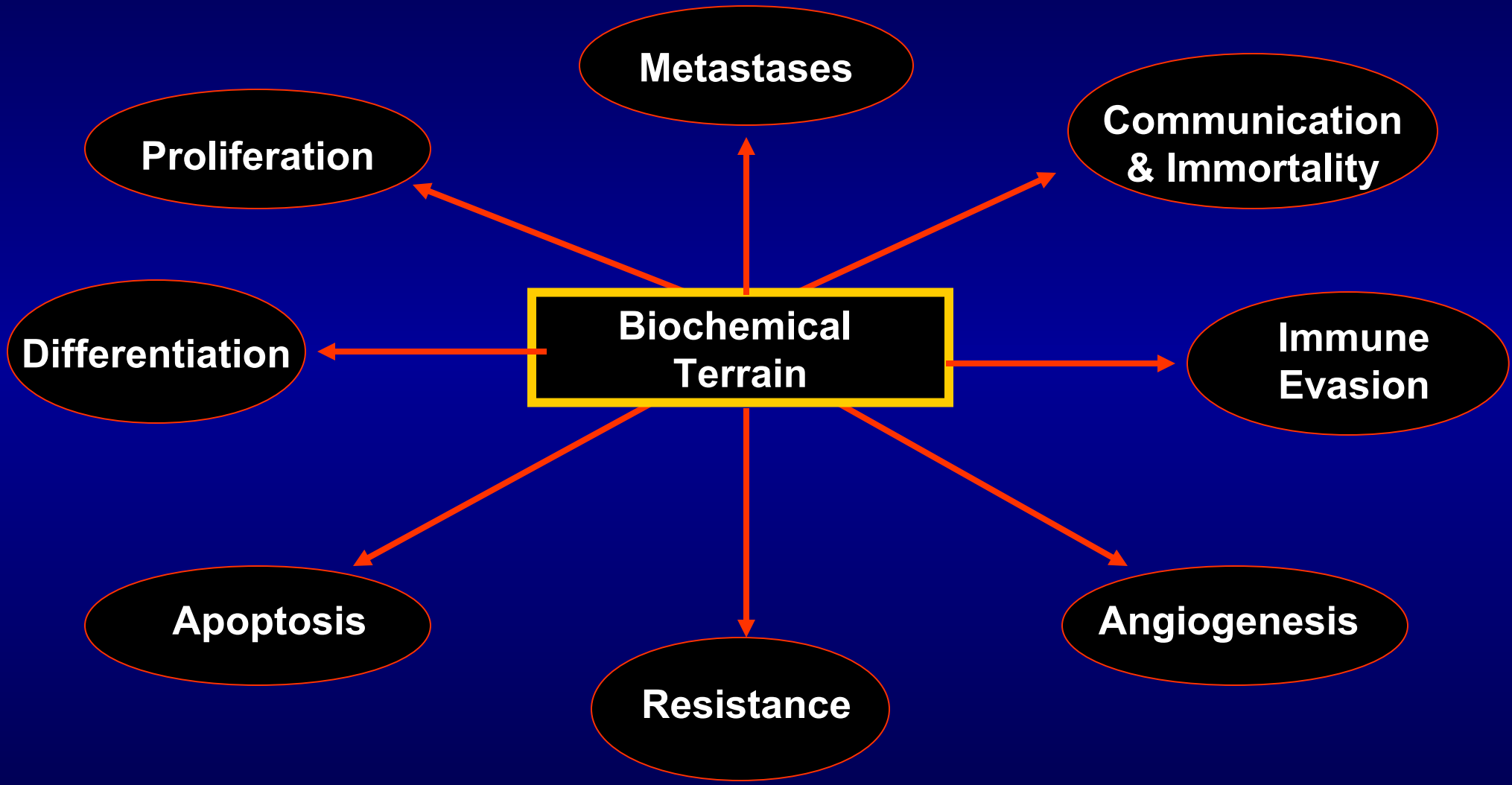
Biochemical Hallmarks ("Terrain")

Antioxidant ← → Prooxidant

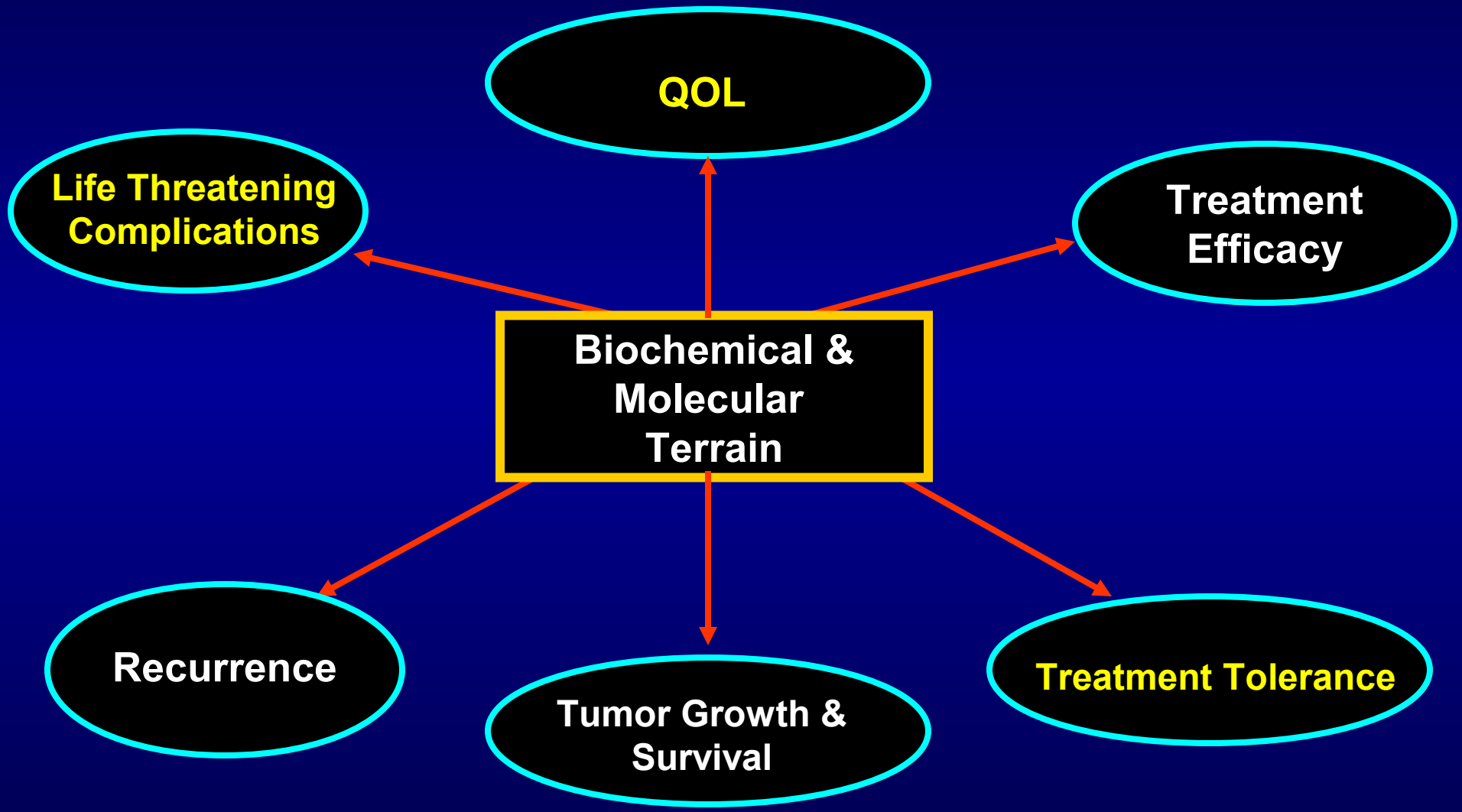


Intracellular & Extracellular Environment Markedly Impacts Supplement effect!

Biochemical Terrain ↔ Tumor Progression Pathways



Biochemical Terrain ↔ Cancer Challenges



Mapping A Patient's Biochemical & Molecular Terrain

Oxidation: oxidized LDL, total antioxidant capacity

Inflammation: C-reactive protein, fibrinogen

Insulin-IGF Axis: FBG, OGT, IGF-1

Stress Chemistry: Cortisol, melatonin

Coagulation: fibrinogen, prothrombin fragments

Immune Dysreg: WBC, NK activity, T-cell counts

Molecular: Tissue IHC
Genomic DNA MicroArray

Inflammation, Mortality & Recurrence

N=1183 breast cancer survivors, N=734 ds free post Rx. Stages 0-III.
Serum amyloid A (SAA) and C-reactive protein (CRP), highest vs lowest

Protein	Mortality/Recurrence	HR	p
Highest SAA level	3 x	3.15	<.0001
Highest CRP level	2 x	2.27	<.002

Conclusion:

Breast cancer patients with elevated inflammation following treatment have markedly reduced survival and recurrence.

Pierce et al. J Clin Oncol. 2009, May 26, epub
Yabroff, KR, et al… JNCI 2008, 100 (24) p. 1755-1762 (Projections for 2020 – US population)

Correcting The Terrain

Drug & Nutraceutical Interventions

- **Oxidation** – Antioxidants, Lipoic Acid, CoQ10, Grapeseed extract, Glutathione, Amifostine, Allopurinol
- **Inflammation** –Curcumin, Boswellia, Fish Oil, Ginger, Stinging Nettles, Bromolein, Ibuprofen, Celebrex, …
- **Insulin Dysregulation** – Soy Isoflavones, Cinnamon, Chromium, Bitter Melon, Metformin
- **Stress Disruption** – Melatonin, Valerian, 5HTP, Rhodiola, L-Theonine, Phosphatidyl Serine
- **Coagulation** – Garlic, Resveratrol, Enzymes, Nattokinase, Vitamin E, Bromolein, Coumadin, Abciximab (Reopro)
- **Immune Imbalance** – Astragalus, Medicinal mushrooms, Beta-Glucans, Zinc, IP6, Arabinogalactans, Cimetidine
- **Molecular Profiling** – IHC: EGFR – soy isoflavones, VEGF – green tea, Cox-2 - curcumin
  - » Genomics: GATA-1 – Sulforaphane, ELF4 – Apigenin, …

Metastatic Ovarian Cancer -- 46 yr old active climber

1995 Initial diagnosis

1997 Started at Block Center (Chemotherapy, Molecular, Immunotherapy)

***Patient's Condition*:**

- Marked inflammation and fatigue

Block Center Integrative Treatment Program:

▪ Full Training	→ Tailored nutrition, fitness, stress care
▪ Abd w/ swelling	→ Enzymes
▪ Neuropathy	→ Thioctic acid, Acetyl-L-Carnitine
▪ Cortisol – flat-lined	→ **Ginseng, ACBA**

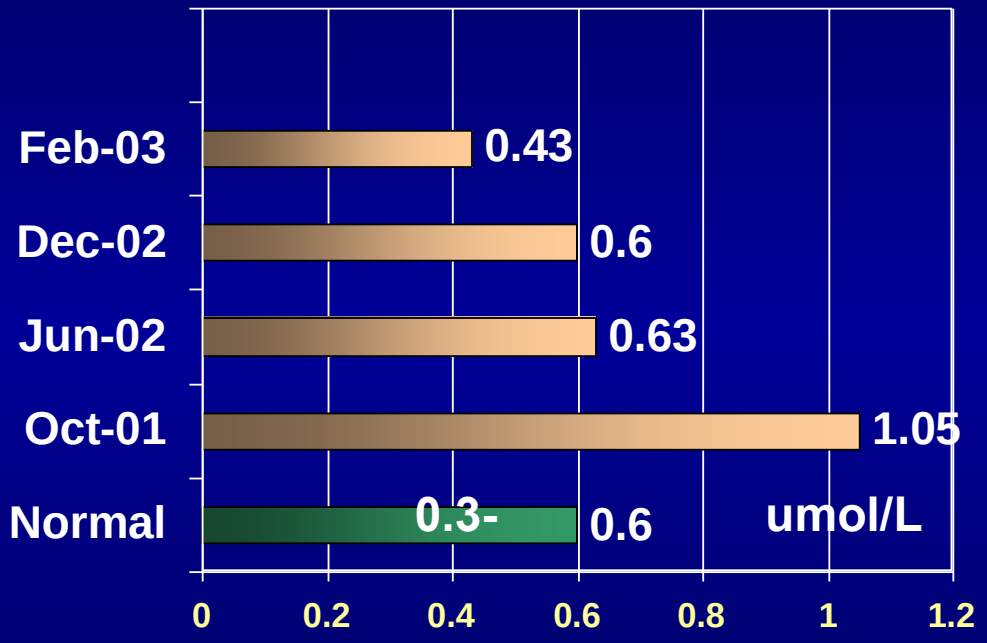
Anti-inflammatory Intervention

- Fish Oil
- Curcumin
- Green tea catechins

2009: 14 years out since diagnosis

LIPID PEROXIDES

46 y/o woman, an active climber – Metastatic Ovarian Cancer



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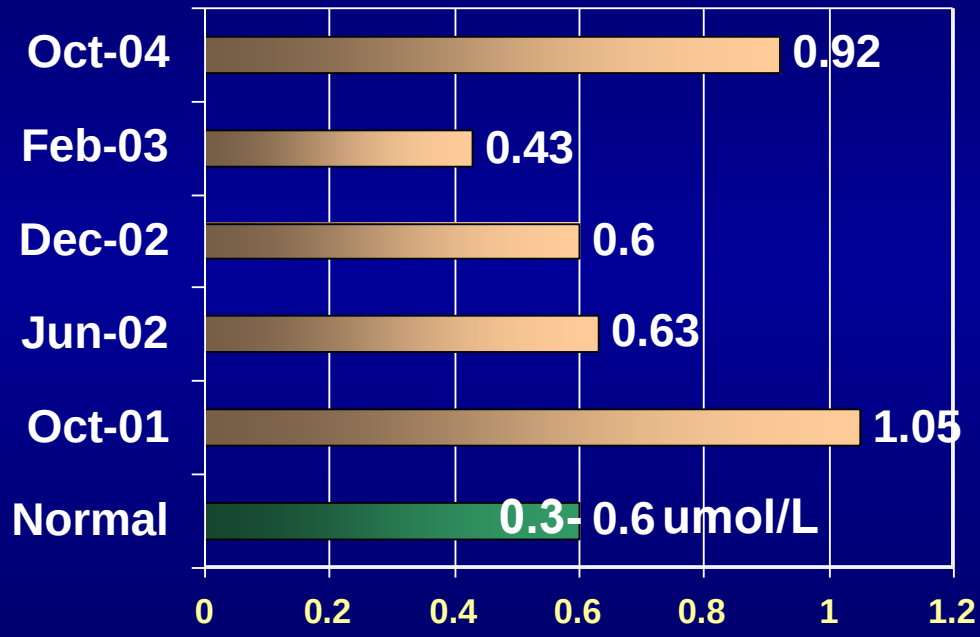
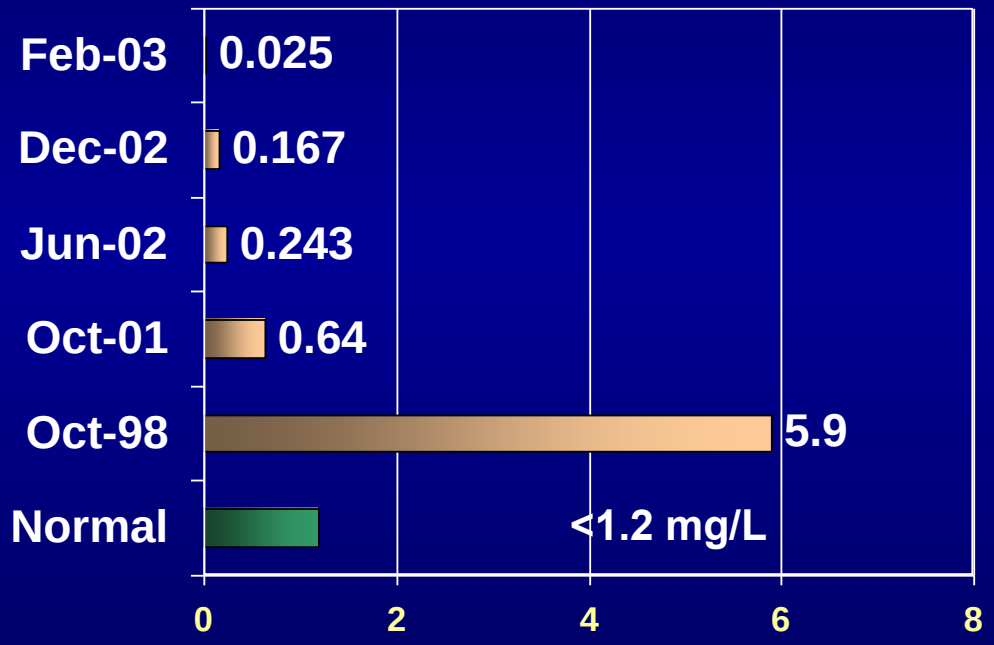


HS-CRP

High-Sensitive CRP

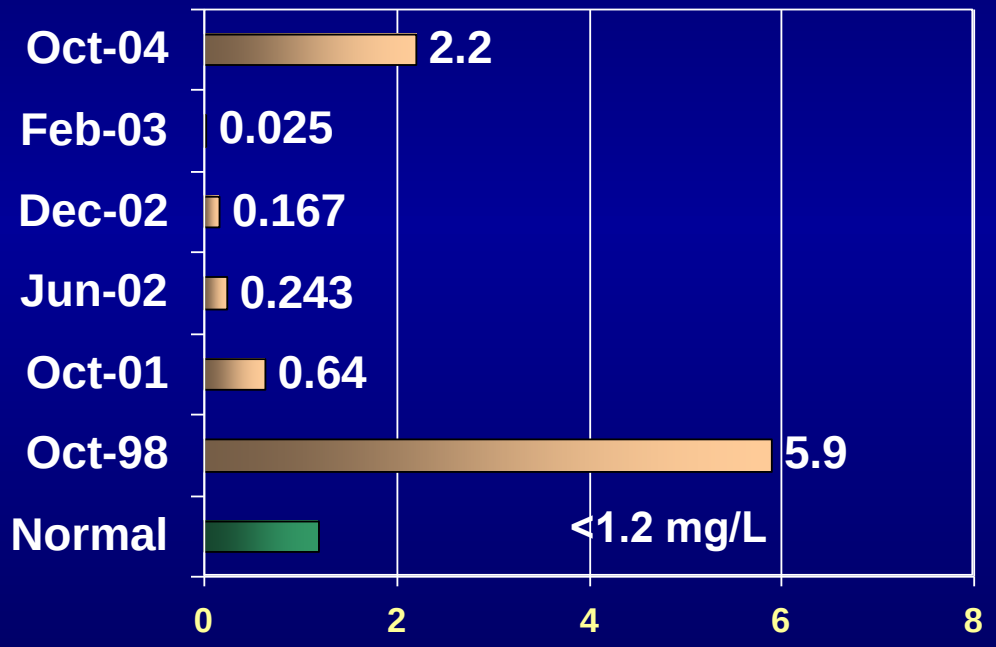
46 y/o woman, an active climber – Metastatic Ovarian Cancer



HS-CRP

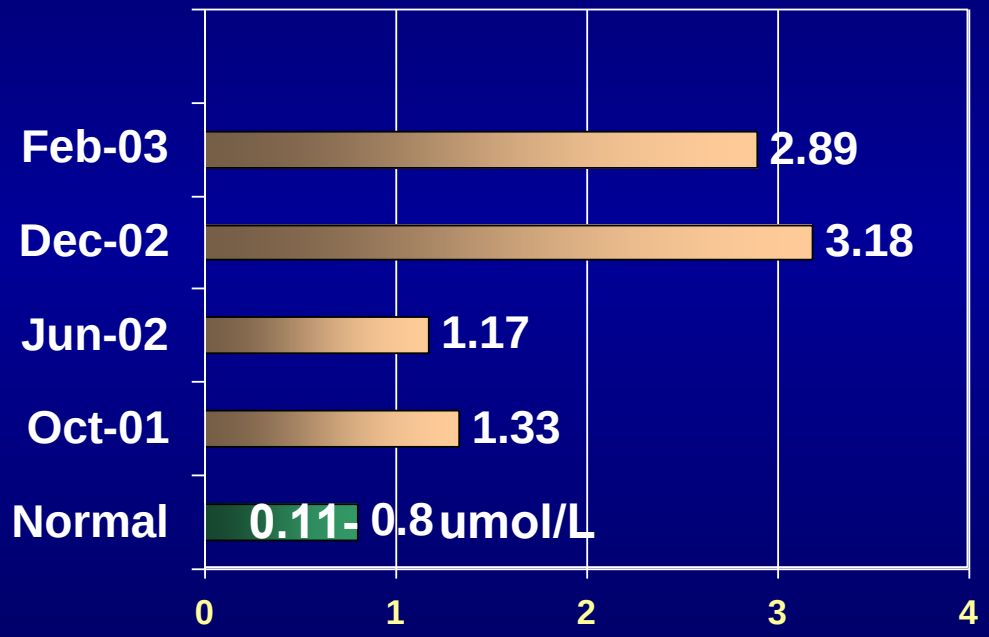
High-Sensitive CRP

46 y/o woman, an active climber – Metastatic Ovarian Cancer



LYCOPENE

46 y/o woman, an active climber – Metastatic Ovarian Cancer



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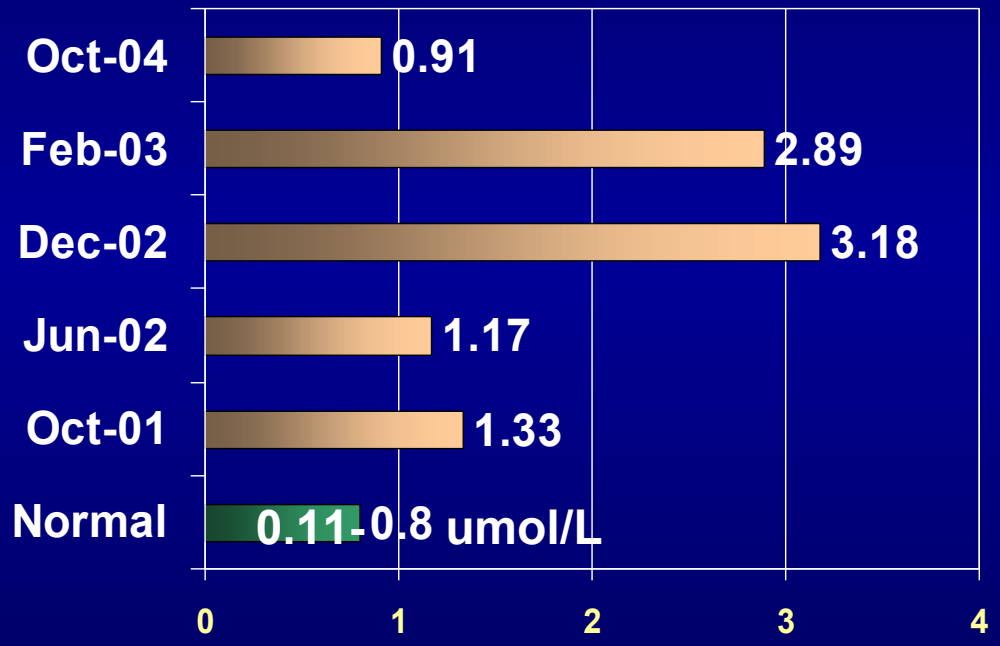
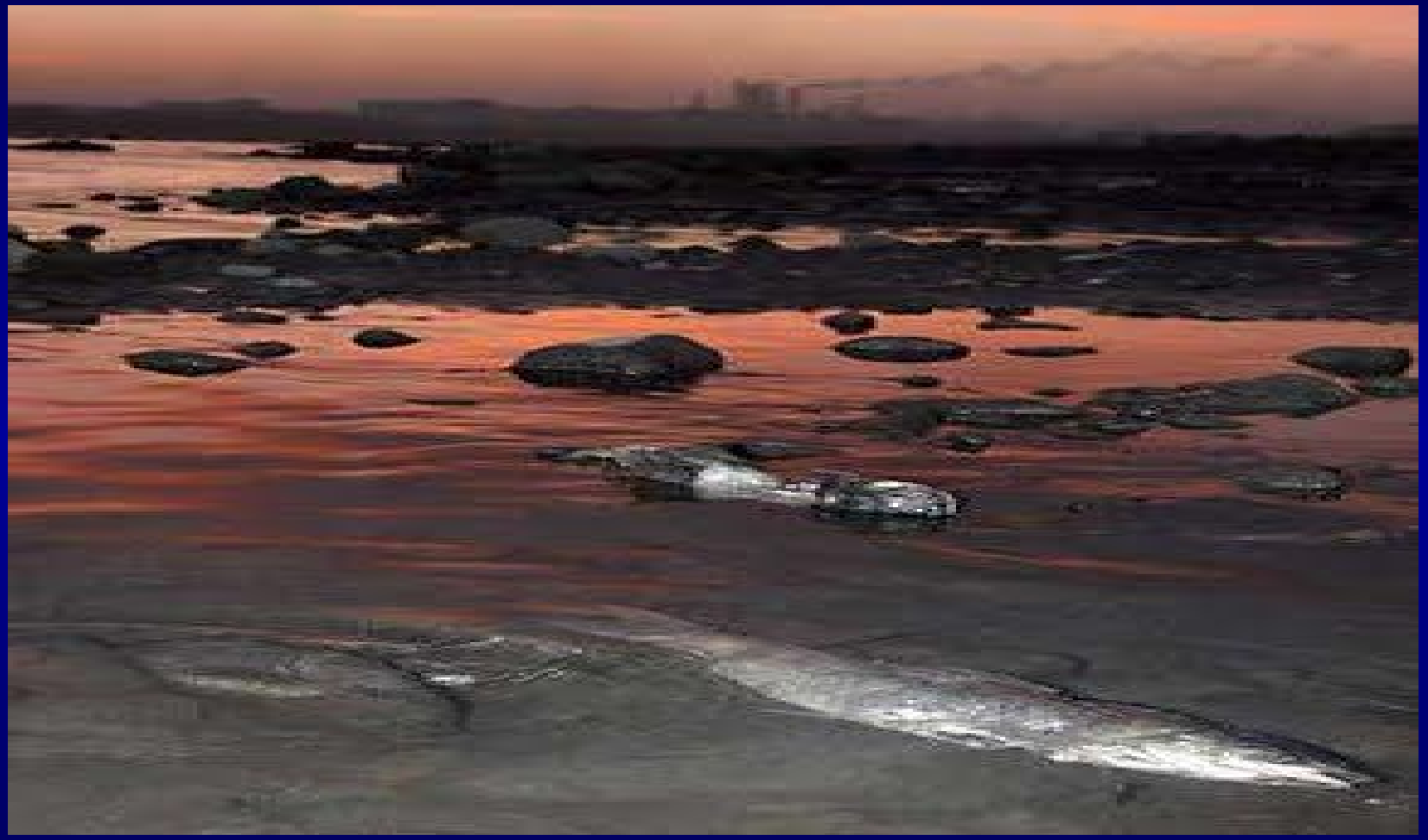


trick

14 yrs

Met Ovarian Ca

Antioxidants – Chemotherapy Debate



It is unwise to prescribe antioxidants or any supplement regimen, without first assessing & correcting disruptions in a patient's terrain.

REACTIVE OXYGEN SPECIES CONTRIBUTORS

INCREASED OXIDATIVE STRESS

- ↑ Unbound Fe & Cu → ROS
- Chronic inflammation
- Heme iron intake (meat)
- Vit C xs (*Fenton Reaction*)

Superoxide radical —*SOD*→ H_2O_2 —*Catalase + GPx*→ H_2O

- Overactive Immune Function
- Overactive Phase 1 Detox
- Respiratory Burst

- Poor intake exogenous AOXs
  - •Low Intake plant-based aox
  - •XS intake of labile antioxs

- Endogenous Enzymes –
  - •Polymorphisms
  - •Epigenetic changes
  - •Cofactors (Mn, Zn, Se)
  - •Glutathione synthesis
  - •SOD/Catalase - GPx Ratio

- Hazardous Diet
- Tobacco + Alcohol
- Obesity
- Inactivity
- Overexertion
- Distress
- Circadian Disruption

- Aerobic cellular respiration
- Environmental factors

CANCER

WHY ANTIOXIDANTS?
OXIDATIVE STRESS DRIVES MALIGNANT GROWTH

- Tumors, Treatment, Lifestyle, Genetics … → generate ↑ ROS
- ROS:
  - → Damage tissues[1]
  - → Damage endothelial cells which can promote dissemination[2]
  - → Disrupt endogenous antioxidant systems[1]
  - → Promote tumor angiogenesis[3]
  - → Drive mutation resulting in more aggressive malignant clones[4,5]
  - → Drive growth signaling molecules → proliferation and apoptosis[6]

❖ *ROS-induced DNA damage is proportional to metastatic growth & progression*[7]

Chemotherapy: Degree of Oxidative Mechanism

Mainly oxidative (ROS generating):

- alkylating agents - melphalan, cyclophosphamide
- anthracyclines - doxorubicin, epirubicin
- podophyllin derivatives - etoposide
- platinum complexes - cisplatin, carboplatin
- camptothecins - topotecan, irinotecan

Moderately oxidative:

- taxanes - paclitaxel, docetaxel
- vinca alkaloids - vincristine, vinblastine
- antimetabolites - methotrexate, fluorouracil, cytarabine

Not oxidative:

- asparaginase and dactinomycin

Antioxidant Mechanisms

Free radical scavengers (reduction or breaking lipid chains):

- melatonin, NAC, Vitamin E, GSH, beta carotene and vitamin C

Antioxidant enzymes (form selenoproteins):

- selenium, GSH

Metal chelators:

- Vitamin C, EGCG

Cellular protectors (from free radical attack):

- Vitamins A, C, E, melatonin

DNA aberration repair

- EGCG

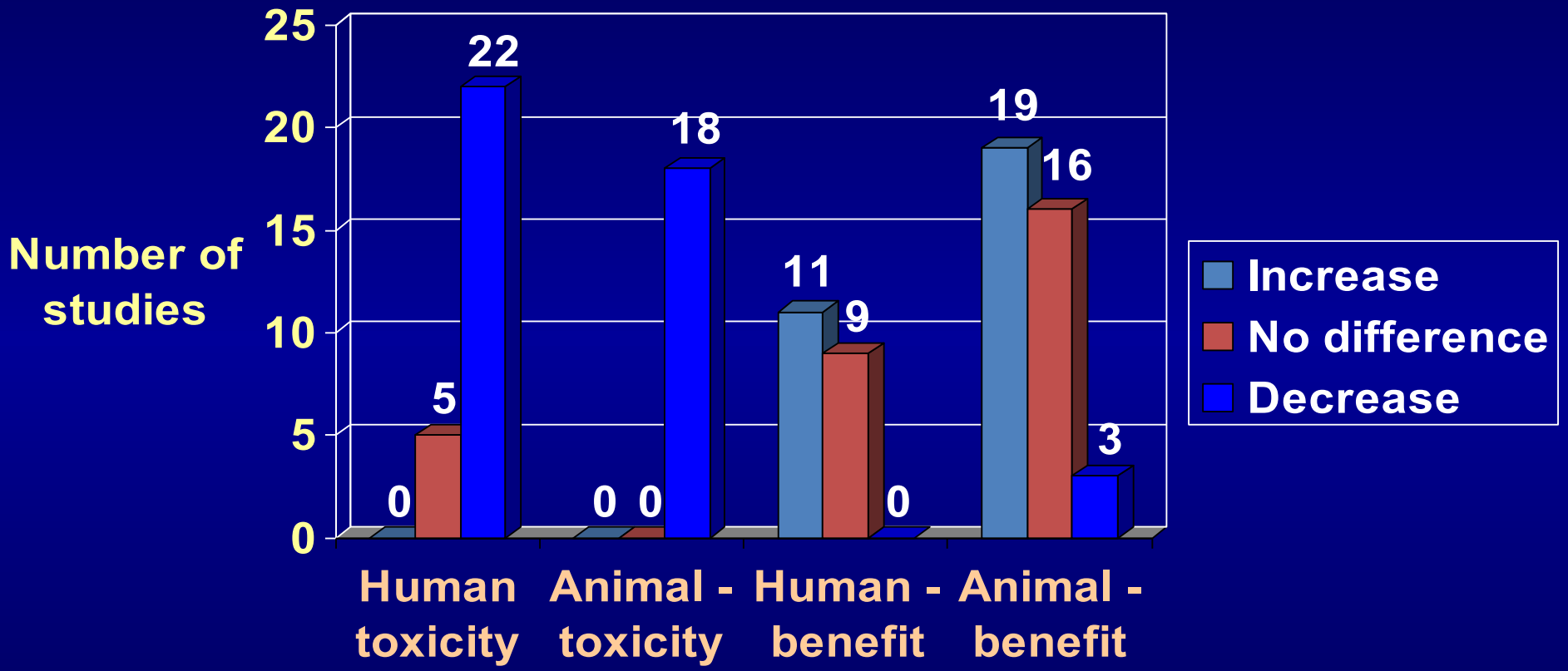
Chemotherapy and Toxicity

- Many chemotherapies kill cancer cells through an ROS apoptotic mechanism.
- ROS are often responsible for serious treatment-related side effects.
- Examples:
  - platinums - neurotoxicity/neuropathy
  - anthracyclines – cardiotoxicity
  - radiation – proctitis, diarrhea, bleeding, pain and fecal incontinence
- Cancer patients often have low levels of systemic antioxidants.

  Levels drop even lower after treatment.

Co-administration of Antioxidants and Conventional Treatment, Based on Literature Review[1]

Reviewed all conventional treatments (chemo, radiation, tamoxifen)



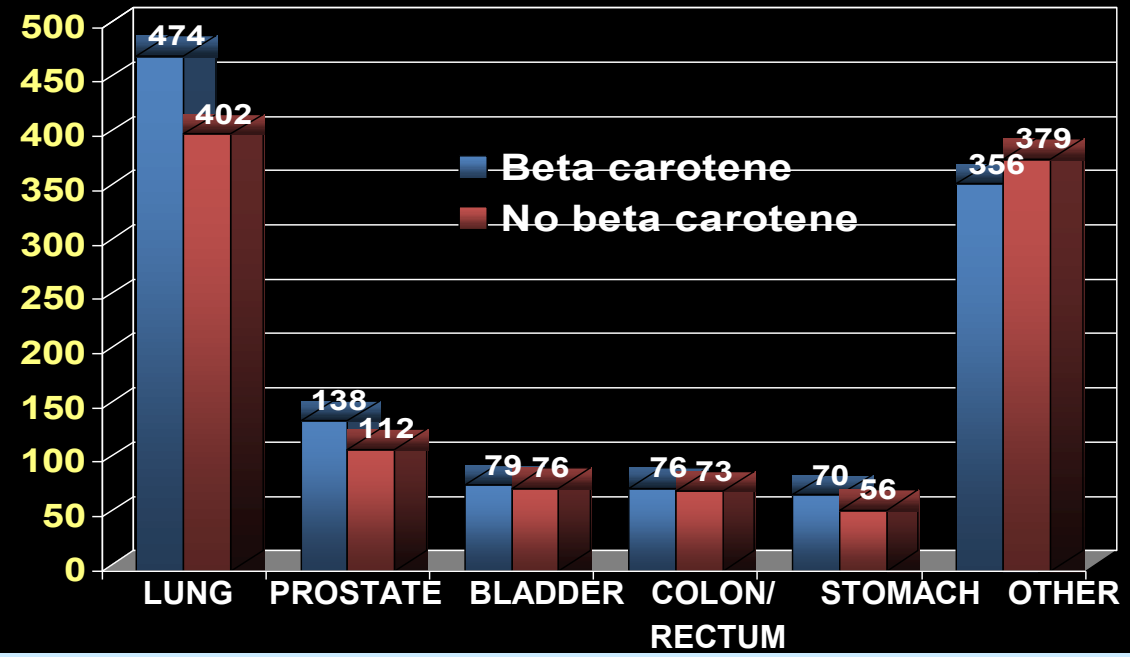
Lamson & Brignall, 1999 "It's time to research the role of supplements rather than dismiss them."

Later: R. Moss "…it serves neither the scientific community nor the burgeoning population of cancer patients."

History of Debate

CARET: lung ca↑ from beta-carotene supp.[1].

Randomized: 1st report: Beta carotene → ↑ in lung, prostate & stomach cancer
In Finland, 29,133 men (age 50-69 yrs) studied for 5-8 years[1,2,3]



However: **Impact of subjects' biochemical environment was ignored → Smokers!**
Revealed labile redox → Pro-oxidant feature of B-carotene (~ synthetic, single nutrient).

History of Discussion

2002
Labriola & Livingston: antioxidants may interfere, counteract chemoth killing effects.[2] Overreliance on mechanistic & preclinical data.

2004
Ladas: noted antioxidant levels decline after chemotherapy.[1] Important documentation of chemo impact but review didn't examine interference.

2005
D'Andrea: brief review asserts avoid antioxidants w/ chemotherapy.[2] Excess reliance mostly preclinical evidence, limited clinical. ("Do No Harm," → but giving chemoth?)

2007
Simone: review of clinical trials concludes antioxidants don't compromise chemoth or radiation.[3,4] Included observational trials in assessment.

History of Discussion

2008

Lawenda et al reviewed studies of antioxidants in radiation and chemotherapy.[1]

Conclusions:

-Avoid antioxidants with radiotherapy

-Avoid antioxidants with chemotherapy – but no data provided to support position.

2009

Block et al letter to editor, JNCI -- critiqued and challenged Lawenda's conclusions

-Avoid antioxidants with radiotherapy – HOWEVER, their data was limited. Mostly relied on Bairati's first *flawed* study. Did not discuss corrections & retraction in second paper.

-Avoid antioxidants with chemotherapy – HOWEVER, their own data showed no harm and in fact, some benefit, but paper and conclusion did not reflect this.

What Makes the News? *"Supplements are Harmful!"*

β-carotene and radiation therapy[1,2]

RCT, N= 540, Stages I-II head/neck cancer, Rx radiation
β-carotene, α-tocopherol or placebo.

HRs for recurrence/mortality (p<.05)

Variable	Original
Recurrence	1.86
All-cause mortality	1.38
Cancer mortality	ns

Original data made headline news internationally!

But erroneous conclusion!

Resulted in profound damage to supplement image and use globally!

From HEADLINES TO NO-LINES → flawed initial interpretation IGNORED!

RCT, N= 540, Stages I-II head/neck cancer, Rx radiation,
β-carotene, α-tocopherol or placebo.

Re-analysis Nov. 2006

HRs for recurrence/mortality (p<.05)

Variable	Original	Smokers	Non-smokers
Recurrence	1.86	2.41	ns
All-cause mortality	1.38	2.26	ns
Cancer mortality	ns	3.38	ns

- Only smoking ***concurrent*** with radiation → >100% ↑ in recurrence and mortality.
- **Non-smokers** or even **smoking before and after radiation** had **NO ADVERSE IMPACT!**
- Recent ASCO & AACR presentations continue to ignore re-evaluation and new results.
- Results demonstrate importance of the terrain and impact on agent's redox stability.
- Flawed study interpretation damaged supplement image and use globally!
- - Radiation therapy induced breast cancer stem cells → 30 fold ↑ *in tumor formation.*

Concurrent Use Of Antioxidants & Chemotherapies:
THE GREAT DEBATE

Question:
What is the effect of antioxidant supplementation in patients on chemotherapy?

a) Increase/decrease efficacy of anticancer agents
b) Protect normal tissue
c) Reduce toxicity
d) Protect cancer cells from chemotherapy
e) None of the above

Our research group has held an ongoing review on antioxidants for the past decade:

Two Systematic Reviews of RCTs[1,2]

2007:

Impact of Antioxidant Supplementation on Chemotherapeutic Efficacy

Cancer Treat Rev. 2007 Aug;33(5):407-18

2008:

Impact of Antioxidant Supplementation on Chemotherapeutic Toxicity

Int J Cancer 2008 Sep 15;123(6):1227-39

Keith Block[1], Amanda Koch[1], Mark Mead[1], Peter Tothy[1], Robert Newman[2], and Charlotte Gyllenhaal[1]

[1] Institute for Integrative Cancer Research and Education, Evanston, IL

[2] MD Anderson Cancer Center, Houston, TX

Inclusion Criteria, Combined for Both Systematic Reviews

Type of Study:

- Only randomized, controlled trials (RCT's).
- Only studies reporting data with antioxidant impact on chemotherapy toxicity, response or survival.

Study Population:

- Cancer patients currently receiving chemotherapy with ROS mech of action
- No concurrent radiation therapy
- All cancer types included

Treatment Intervention Analyzed:

- Supplements given concurrently with chemotherapy.
- No synthetic, whole herbs, or multi-ingredient supplements.

Search Terms

ROS-generating chemotherapies:

- doxorubicin, epirubicin, daunorubicin, idarubicin, cisplatin, carboplatin, oxaliplatin, bleomycin, carmustine, cyclophosphamide, melphalan, etoposide, mitomycin, vinblastine, vinorelbine, paclitaxel, docetaxel

Antioxidant compounds:

- vitamin C, vitamin E, vitamin A, melatonin, glutathione, N-acetylcysteine, polyphenols, green tea catechins, carotenoids, carnitine, selenium, ellagic acid, curcumin, coenzyme Q10, lycopene, flavonoids, and isoflavones, including chemical names and synonyms of vitamin names.

Whole herbs or herbs plus above antioxidant compounds:

- Not included; confounding variables due to non-antioxidant mechanisms from multiple phytochemicals in botanicals.

Antioxidants And Chemo *Interference*

Systematic Literature Review

845 articles screened included → 33 RCTs

N = 1554

Dates: 1966 -- Dec. 2006 – All languages included

Databases searched (# results):	
Medline	368
CENTRAL (Cochrane)	284
CinAhl	90
AMED / Althealthwatch	254
EMBASE	85

Number of terms included:	
Cancer	5
Chemotherapy	24
Antioxidants	32

Antioxidants And Chemo *Toxicity*

Systematic Literature Review

965 articles screened included → 33 RCTs

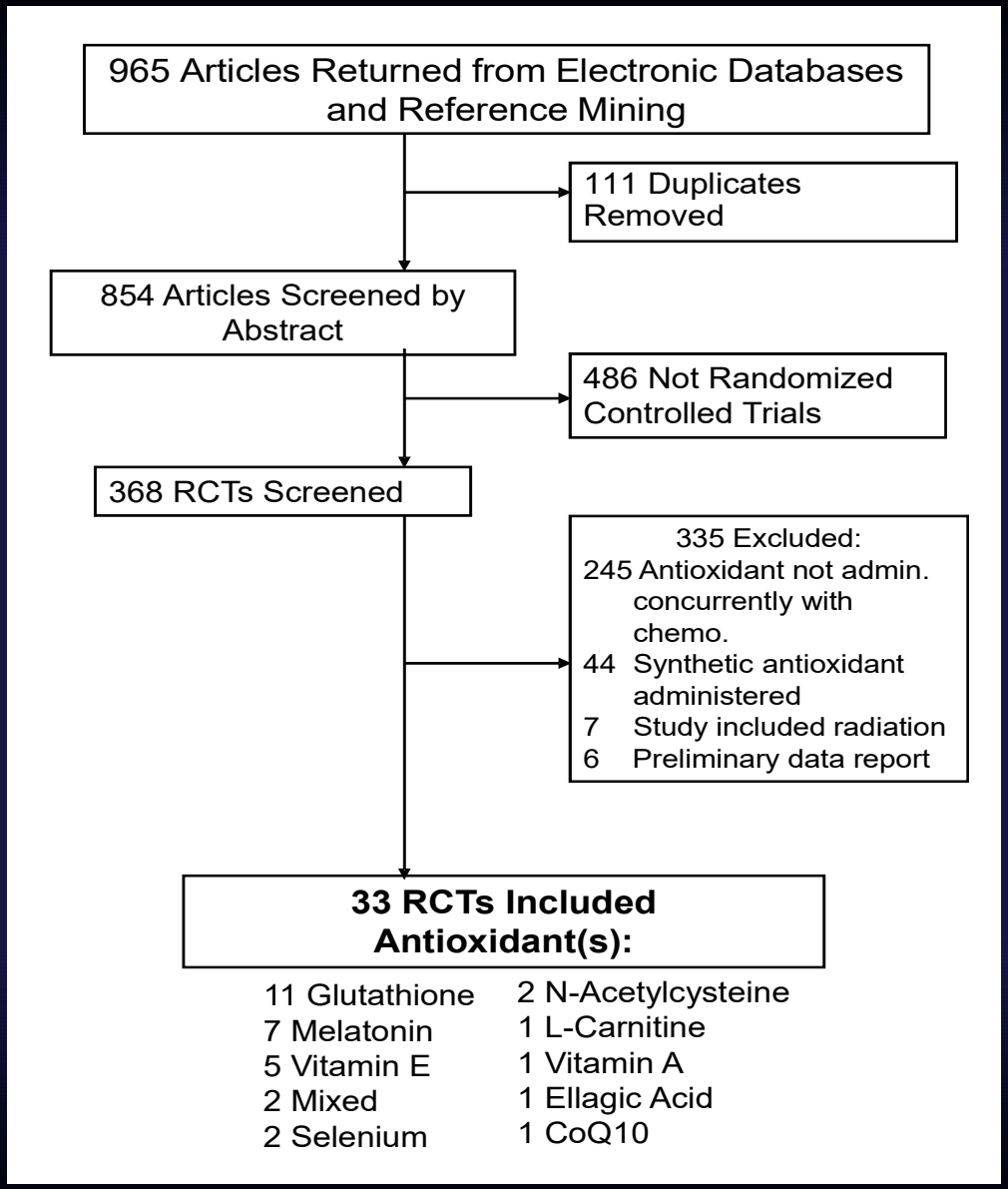
N = 2446

Dates: 1966-Oct. 2007 – All languages included

Databases searched (# results):	
Medline	368
CENTRAL (Cochrane)	284
CinAhl	90
AMED / Althealthwatch	254
EMBASE	85

Number of terms included:	
Cancer	5
Chemotherapy	24
Antioxidants	32

Example Flow Chart Of Exclusion Process For Systematic Review (original study, toxicity)



Overview of Results[1,2]

Author	Year	No. Pts, cancer type	Supplement	Decreased side effects	Increased survival	Higher response rate	Quality (Jadad)
Cascinu	2002	52, CRC	GSH	Yes*	No Difference	No difference	5
Cascinu	1995	50, Gastric	GSH	Yes*	Yes	Yes	5
Schmidinger	2000	20, NSCLC, HNC	GSH	Yes*	Yes	Yes	2
Smyth	1997	151, Ovarian	GSH	Yes	No Difference	Yes	5
Bogliun	1996	54, Ovarian	GSH	Yes	n/a	Yes	1
Colombo	1995	33, Ovarian	GSH	Yes	Yes	Yes	2
Parnis	1995	24, Ovarian	GSH	No Difference	n/a	n/a	2
Catalan	2001	52, CRC	GSH	Yes*	n/a	n/a	2
Fujimoto	1983	207, Gastric	GSH	No Difference	No Difference	n/a	1
Choi	2007	51, various	GSH	Yes*	n/a	n/a	2
Wang	2007	86, CRC	GSH	Yes*	No Difference	No difference	1
Lissoni	2003	100, NSCLC	MLT	Yes*	Yes	Yes*	1
Lissoni	1999	250, various	MLT	Yes*	Yes*	Yes*	3
Lissoni	1997a	80, various	MLT	Yes	n/a	n/a	1
Lissoni	1997b	70, NSCLC	MLT	Yes*	Yes*	Yes	1
Lissoni	2007	370, NSCLC or GI	MLT	Yes*	Yes*	Yes*	1
Cerea	2003	30, CRC	MLT	Yes	n/a	Yes	2
Ghielmini	1999	20, Lung	MLT	No Difference	n/a	n/a	3
Pathak	2005	136, NSCLC	Mix	No Difference	Yes	Yes	2
Falsaperla	2005	48, Prostate	EA	Yes*	Yes	Yes	2
Weijl	2004	48, various	Mix	No	n/a	Yes	4
Meyskens	1995	124, CML	Vit A	No*	Yes	n/a	2
Myers	1983	24, various	NAC	No	n/a	Yes	2
Lin	2006	14, CRC	NAC	Yes*	n/a	n/a	1
Waldner	2006	40, NHL	L-Carnitine	No Difference	n/a	n/a	1
Iarussi	1994	20, NHL or Leukemia	CoQ10	Yes	n/a	n/a	2
Sieja	2004	62, Ovarian	Selenium	Yes*	n/a	n/a	2
Federico	2001	60, GI	Selenium	Yes*	n/a	n/a	1
Pace	2003	27, various	Vit E	Yes*	n/a	No	2
Wadleigh	1992	18, various	Vit E	Yes*	n/a	n/a	2
Whittaker	1984	63, Leukemia	Vit E	No Difference	n/a	n/a	1
Argyriou	2006a	30, various	Vit E	Yes*	n/a	n/a	3
Argyriou	2006b	32, various	Vit E	Yes*	n/a	n/a	2

NHL= Lymphoma; GSH=glutathione; MLT=melatonin; EA=ellagic acid; NAC=n-acetyl cysteine

Effects of Antioxidants on *Response* to Chemo

Antioxidant (chemo)	# Reports	Decreased Response	No Difference	Increased Response
Glutathione (platins, mito-C)	7	0	6	1
Melatonin (platins, CPT-11)	4	0	1	4
Other* (platins, cycloph, others)	8	0	8	0

*Ascorbic acid 3, Vitamin A 2, Vitamin E, NAC, ellagic acid, one each (none from update studies)

There was no evidence of a decrease in treatment response from the addition of antioxidants.

Effects of Antioxidants on *Survival*

Antioxidant (chemo)	# Reports	Decreased Survival	No Difference	Increased Survival
Glutathione (platins, mito-C)	6	0	6	0
Melatonin (platins, CPT-11)	3	0	0	4
Other* (platins, cycloph, others)	3	0	3	0

*Ascorbic acid 3, Vitamin A 2, Vitamin E, NAC, ellagic acid, lycopene, 1 each

There was no evidence of a decrease in survival from the addition of antioxidants.

Effects on Toxicity: AOX vs Control Arm; Combined Data with Updates

Toxicity	# Reports	Decreased Tox	No Difference	Increased Tox
Neurotoxicity*	23	17(14 sig) **	6	0
Myelosuppression	17	8 (8 sig)	9	0
Alopecia	10	2 (1 sig)	7	1
Asthenia	7	7 (7 sig)	0	0
Stomat/Mucositis	6	4(3 sig)	2	0
Diarrhea	5	1	3	1
N/V	5	1	4	0
Weight loss	5	4(4 sig)	1	0
Cardiotoxicity	4	2 (2 sig)	2	0
Nephrotoxicity	3	1(1 sig)	2	0
Ototoxicity*	4	1	3	0
Oliguria	1	1	0	0
General*	1	0	0	1 (1sig)

There was consistent evidence of a decrease in toxicity from the addition of antioxidants.

Reports of Increased Toxicity with Anti-oxidants & ChemoRx

- There were 49 separate reports of decreased toxicities (40 significant), 39 with no differences and 3 with increased toxicity.
- Only one trial - Vit A – statistically significant increase in toxicity among the antioxidant vs control group. Common with Vit A. And control had increased risk of disease progression and death.
- In another study (NAC-containing mixture), two of eight toxicities measured were higher in AOX arm (diarrhea, alopecia), but not statisticaly significant.
- Overall, the large majority of studies reported that antioxidants reduced chemotherapy toxicity without interfering with efficacy.

Study Limitations Should Temper Recommendations

- The studies included a variety of cancers and tumor types with small sample sizes (no meta-analysis).
- Inconsistent design with some of the studies detecting differences in toxicity and efficacy.
- Many patients had advanced or relapsed disease; limits ability to generalize data to less advanced patients.
- Jadad scores were low (2's, 3's), indicating a limit of studies that included double-blinding or proper randomization techniques

Clinical Implications of Results

- Antioxidants *enhanced treatment outcomes*. ↑'d survival times, ↑'d tumor response or *both* -- in all but one (not statistically significant*)
- The vast majority** of studies showed antioxidants addition *decreased toxicities.*
- *No trials reported*** a significant *decrease in chemotherapy efficacy* (suggesting *no evidence of interference).*
- *No clinical trial evidence to date suggests a negative effect of antioxidants on chemotherapeutic efficacy.*
- Future research should employ larger sample sizes, better research designs & look at early stages of cancer.

(* this one, Vitamin E, not statistically significant).

(Others lacked statistical power due to small sample sizes, e.g. vit A study)**

Vitamin E Studies

All Vitamin E investigations of neurotoxicity found a statistically significant decrease in neurotoxicity in the antioxidant group. Statistically significant results in yellow.

Reference	Antioxidant Supplement	Patients and Cancer Type	Toxicities in antiox group vs control group
Wadleigh et al, 1992[1]	Vitamin E, no dose given	n=18	33% vs 75% ($p<0.05$) neutropenia**
Pace et al, 2003[2]	Vitamin E 300mg/day orally b/f chemo; con't 3 mos after treatment	n=27 various malignant tumors	31% vs 86% ($p<0.01$) neurotoxicity
Argyriou et al, 2006[3]	Vitamin E 600mg/day during chemo and for 3 months after	n=31 various cancers	21% vs 69% ($p=0.026$) neurotoxicity
Argyriou et al, 2006[4]	Vitamin E 300mg/2x a day	n=32 solid or non-myeloid malignancy	19% vs 63% ($p=0.03$) neurotoxicity

Glutathione Studies

- Majority were platinum-based treatments analyzing reduction of toxicity.
- All GSH studies had the same or lower incidence of toxicities in the GSH group versus the control.

Reference	Patients and cancer type	GSH dose (over 15 min, immed. b/f chemo)	Responses in GSH group vs. control	Toxicity in GSH group vs. control
Cascinu et al, 1995[1]	n=50 advanced gastric	1500 mg/m^2	76% vs. 52%	17% vs. 89% neurotoxicity (p=0.0001)
Cascinu et al, 2002[2]	n=52 advanced colorectal	1500 mg/m^2	27% vs. 23%	0% vs. 26% grade 3-4 neurotoxicity (p=0.01)
Smyth et al, 1997[3]	n=151 ovarian (I-IV)	3000 mg/m^2	73% vs. 62%	58% vs. 39% ability to complete chemo (6 cycles) (p=0.04)

Melatonin Studies

- All but one study gave 20 mg melatonin (MLT) doses orally in the evening.
- All but one study reported reduced toxicities in the MLT group, most statistically sig.

Reference	Patients and cancer type	Responses in MLT group vs. control	Toxicity in MLT group vs. control
Lissoni et al, 2003[1]	n=100 advanced NSCLC	35% vs 18% (p=0.05)	Neurotoxicity 18% vs 41% (p<.01), thrombocytopenia 14% vs 20% (p<.01)
Cerea et al, 2003[2]	n=30 metastatic colorectal	36% vs 13%; disease stab. 86% vs 44% (p<0.05)	Occurrence grade 3-4 diarrhea 29% vs 38%
Lissoni et al, 1999[3]	n=250 breast, GI, NHL	34% vs 15% (p<0.001)	Myelosuppression 20% vs 43% (p<.001), Neurotoxicity 2% vs 13% (p<.05), Stomatitis 10% vs 30% (p<.02)
Lissoni et al, 2007[4]	n=370 advanced NSCLC or GI cancer	36% vs 20% (p<.001)	Thrombocytopenia 4% vs 22% (p<.01), Neurotoxicity 5% vs 12% (p<.05)

Other Antioxidant And Chemotherapy Studies

Reference	Antioxidant supplement	Patients and cancer type	Response in antiox group vs control group	Toxicities in antiox group vs control group
Falsaperla et al, 2005[1]	Ellagic Acid 60mg BID orally b/f meals during chemo and after	n=48 prostate	25% vs 0% (no statistical analysis)	33% vs 75% (p<0.05) neutropenia
Meyskens et al, 1994[2]	Vitamin A 50,000 IU/day, as retinol	n=124 melanoma	5-yr survival rates: 48% vs 30%	23% vs 4% (p= 0.002)*** (only study with higher tox in antiox)
Sieja et al, 2004[3]	Selenium	n=62 ovarian cancer	No analysis of response or survival	/ WBC in antiox, plus all other side effects except diarrhea
Lin et al 2006[4]	NAC, oral, 1200mg	n=14 Stage III colon cancer	No analysis of response or survival	Grades 2-4 neuropathy 20% vs 89% (p<.05)

Outline:

Mechanistic considerations of effects of antioxidants on chemotherapy activity: *Prooxidant effects of antioxidants*

1. Interaction with intracellular copper by plant antioxidants causes ROS-mediated DNA breaks: prooxidant effect.

2. Pharmacological levels of antioxidants produce ROS in cancer cells, causing apoptosis: confirming prooxidant effect.

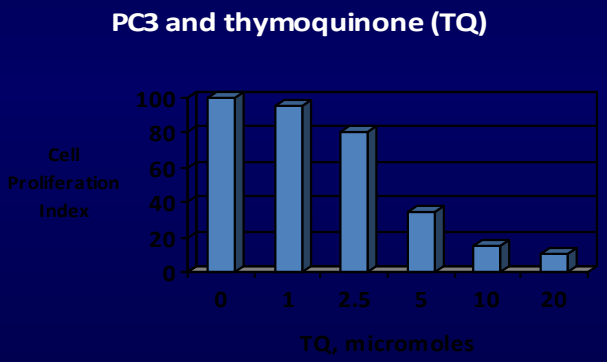
3. IV-vitamin C, apoptosis and chemotherapy

4. IV glutathione and apoptosis

Interaction with intracellular copper

Plant-derived flavonoids, tannins, catechins, quinones, stilbenes and ascorbic acid are antioxidants that exhibit prooxidant DNA damaging properties through interacting with copper in cancer cells but not normal cells (F.H.Sarkar, Karmanos Cancer Institute).

Effects of the antioxidant thymoquinone (TQ), on cancer cells:



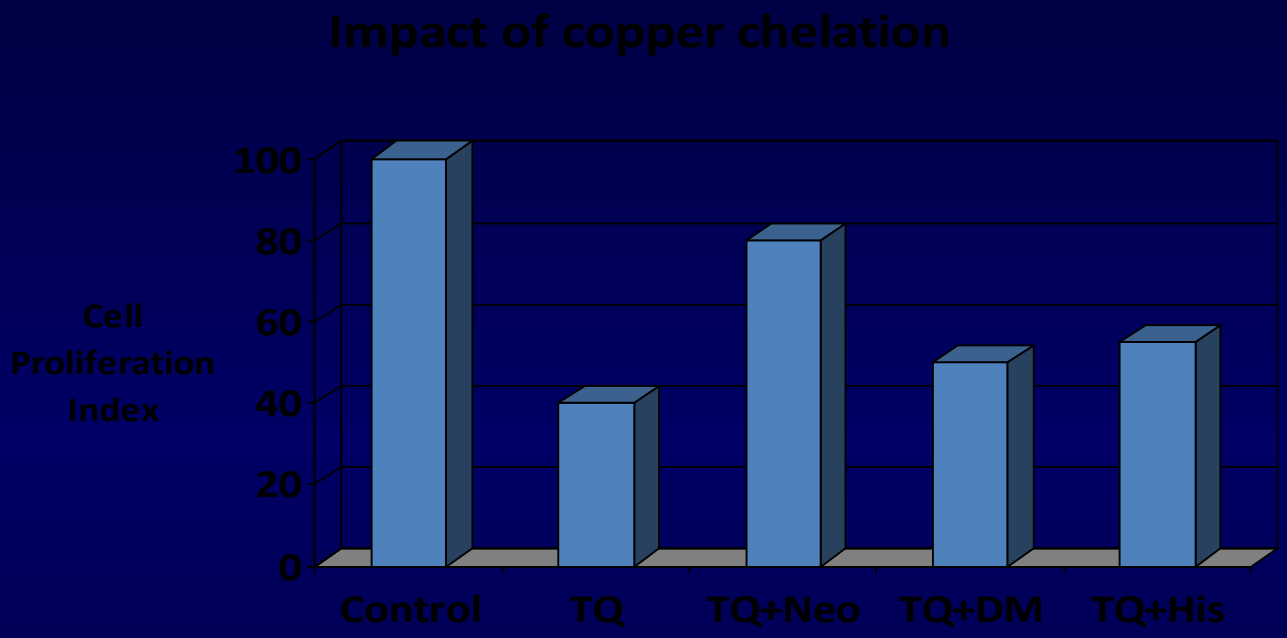
Thymoquinone reduces cell proliferation in PC3 prostate cancer cells.

Effect is due to increased apoptosis.

Prooxidant effect is confirmed through it being counteracted by SOD & catalase.

Zubair, Cell Death and Disease 2013; 4:e660

Copper chelator reduces effect of TQ on PC3 cells



Neo = Neocuproine a Cu chelator; DM = iron chelator, His = Zn chelator

TQ reduces proliferation of PC3 cells; effect is abolished by Cu chelator but not other metal ion chelators. Demonstrating that the ↑'d apoptosis by TQ is mediated by copper.

Zubair, Cell Death and Disease 2013; 4:e660

The Dilemma:
Do antioxidants (AOX) interfere with apoptosis?

Many cancer cells have high levels of ROS for signal transduction, as well as high SOD, Catalase (CAT), etc to protect themselves from their internal ROS levels.

Apoptosis pathways in cancer cells:

Intrinsic: ROS → mitochondrial dysfunction → apoptosis

Extrinsic: ROS → TRAIL + death receptor proteins → apoptosis

One would think that AOX **could** disable the ROS in these pathways.

However it is **well known** that antioxidant phytochemicals cause apoptosis in cancer cells, e.g. curcumin, EGCG, pterostilbene, apigenin.

Experimental investigation of AOX, ROS and apoptosis

Measurement of intracellular levels of ROS:

DCF – dichlorodihydrofluorescien diacetate detects H_2O_2

DHE – dihydroethidium detects O_2.

If either DCF or DHE is ↑'d, it will indicate an increase in H_2O_2 or O_2.

Confirmation of prooxidant mechanism:

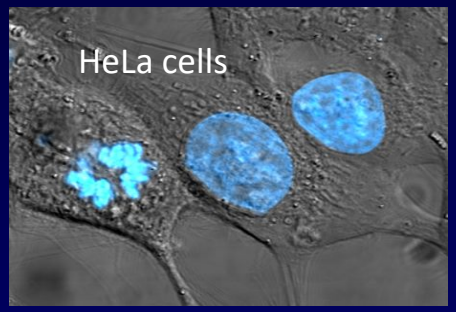
By counteracting intracellular ROS → lowers apoptosis:

Examples: adding AOX such as catalase (CAT), glutathione, SOD, NAC, low dose ascorbic acid (AA).

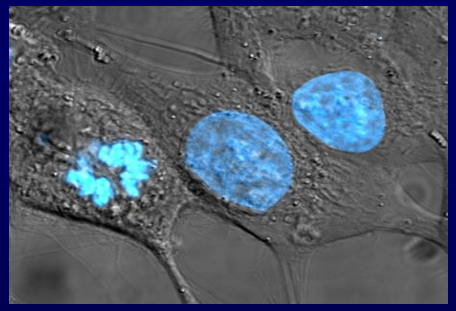
AOX generally must be used at high concentrations (up to millimolar vs micromolar) to achieve this effect in vitro.

Typical Experimental Design

To demonstrate that AOX have ProOx effect → driving apoptosis in cancer cells



+ AOX →? DCF/DHE↑ →? ↑ apoptosis



+ AOX +SOD/CAT/etc →? ↓ apoptosis

+ AOX + chemo →?

Literature review

Search of PubMed for studies of natural AOX + ROS in cancer cells.

Searched article text for mention of DCF/DHE.

For articles showing apoptosis due to AOX, and having DCF/DHE data, we searched for other articles in which same AOX was given with chemotherapy in vitro, in vivo or clinically.

Curcumin and apoptosis

Cell lines: colon cancer

Effect of curcumin on apoptosis: ↑

Effect of curcumin on ROS: ↑

Counteracted by: GSH decreased ROS and thus confirmed apoptosis

Mechanism: curcumin targets miRNAs, decreased transcription of proteins involved in apoptosis

Chemotherapy: Enhances effects of multiple chemotherapies plus radiation, in vitro and in vivo, in multiple cell lines

Ghandy, BMC Cancer 2012; 12:564. Goel, Nutr Cancer 2010: 919-30.

EGCG and apoptosis

Cell lines: several pancreatic ca cell lines plus 1 lung cancer line.

Effect of EGCG on apoptosis: ↑

Effect of EGCG on ROS: DCF ↑

Apoptosis counteracted by: NAC, CAT

Mechanism: ROS act by impacting on the mitochondrial pathway

Chemotherapy: ↑ doxorubicin effect on hepatoma in vivo

↑ doxorubicin effect on prostate in vivo

↑ gemcitabine effect on cholangio in vivo

Note: EGCG inhibited H1200 lung cancer in vitro at IC50 of 20 µM – very high. IC50 in vivo was only 0.15 µM – longer exposure time.

Quanugo, Carcinogenesis 20XX26:958-67; Liang, Int J Oncolg 2010; 37:111-23.

Genistein and apoptosis

Cell lines: glioblastoma and normal astrocytes

Effect of genistein on apoptosis: glioblastoma ↑, normal cells - no effect

Effect of genistein on ROS: DCF ↑

Apoptosis counteracted by: ascorbate decreased apoptosis

Mechanism: ROS activated caspases

Chemotherapy: genistein ↑'d gemcitabine effectc on pancreatic ca in vivo
genistein ↑'d cisplatin, gemcitabine effects on ovarian ca in vitro

Note: AOX generally do not cause apoptosis in normal cells. They have lower ROS than cancer cells and thus are less likely to be raised to pro-apoptotic levels. Cancer cells have high ROS for signal transduction which is needed for proliferation.

Das, Cancer 2010; 116:164-76; Banerjee, Int J Cancer 2007; 120:906-7; Solomon, J Ovarian Res 2008; 1:9.

Antioxidants as prooxidants: results

Antioxidant	Cell line, cancer type	Effect on apoptosis	ROS assay used; effect on ROS levels	Antioxidants used as inhibitors	Mechanisms	Impact on ctx or xrt, in vivo
Alpha-lipoic acid	NCI-460 (lung)	Increased	DCF, DHE Alpha-lipoic increased ROS	NAC, catalase, Decreased apoptosis	Produced mito-chondrial ROS; activated caspases	Leukemia, enhanced doxorubicin in vivo
Gamma-toco-trienol plus TRAIL	HCT116, TRAIL resistant (colon)	Increased apoptosis	DCF Gamma-T increased death receptor	NAC, GSH Decreased death receptor	ROS generated by Gamma-T activated death receptor	Gastric, enhanced capecitabine in vivo
Lycopene phytocomplex	HL-60 (leukemia)	Increased apoptosis	DCF Phytocomplex increased ROS	GSH decreased in cells treated with phyto-complex	ROS ↑ and GHS ↓; mito-chondrial pathway	Prostate, enhanced docetaxel in vivo
Scutellarein	MDA-MB231 (breast) MCF-10A (normal breast)	Cytotoxic effect (mechanism unspecified) No effect	DCF Scutellarein increased superoxide. Slightly increased ROS	NAC, pyruvate Decreased cytotoxicity	Produced mito-chondrial ROS.	Hepatoma, enhanced 5FU in vivo

Other antioxidants, each with a similar prooxidative effect, confirmed by evidence of existing hydrogen peroxide and superoxide resulting in increased apoptosis

- Alpha-lipoic acid
- Apigenin
- Diallyl trisulfide
- EGCG
- Gamma-tocotrienol
- *Ginkgo biloba*
- Luteolin
- Lycopene phytocomplex
- Scutellarein

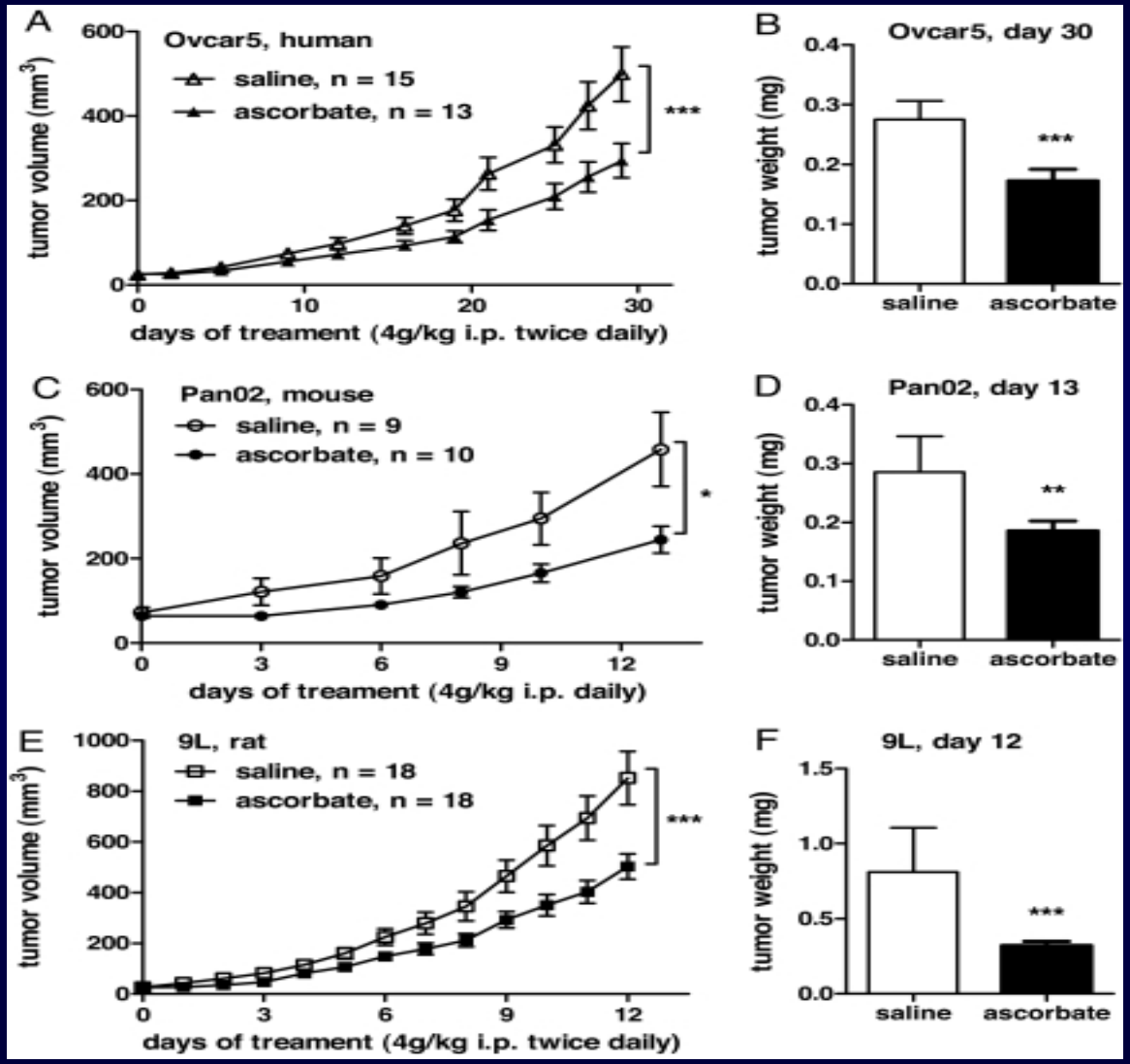
High dose Intravenous vitamin C

Principle: high levels of vitamin C (AA) have cytotoxic effects in cancer cells but not normal cells.

- Blood levels of AA are tightly controlled when it is taken orally, below cytotoxic levels.

- Intravenous administration of doses of 25-50 grams raise blood levels of AA to cytotoxic levels through a pro-oxidative effect.

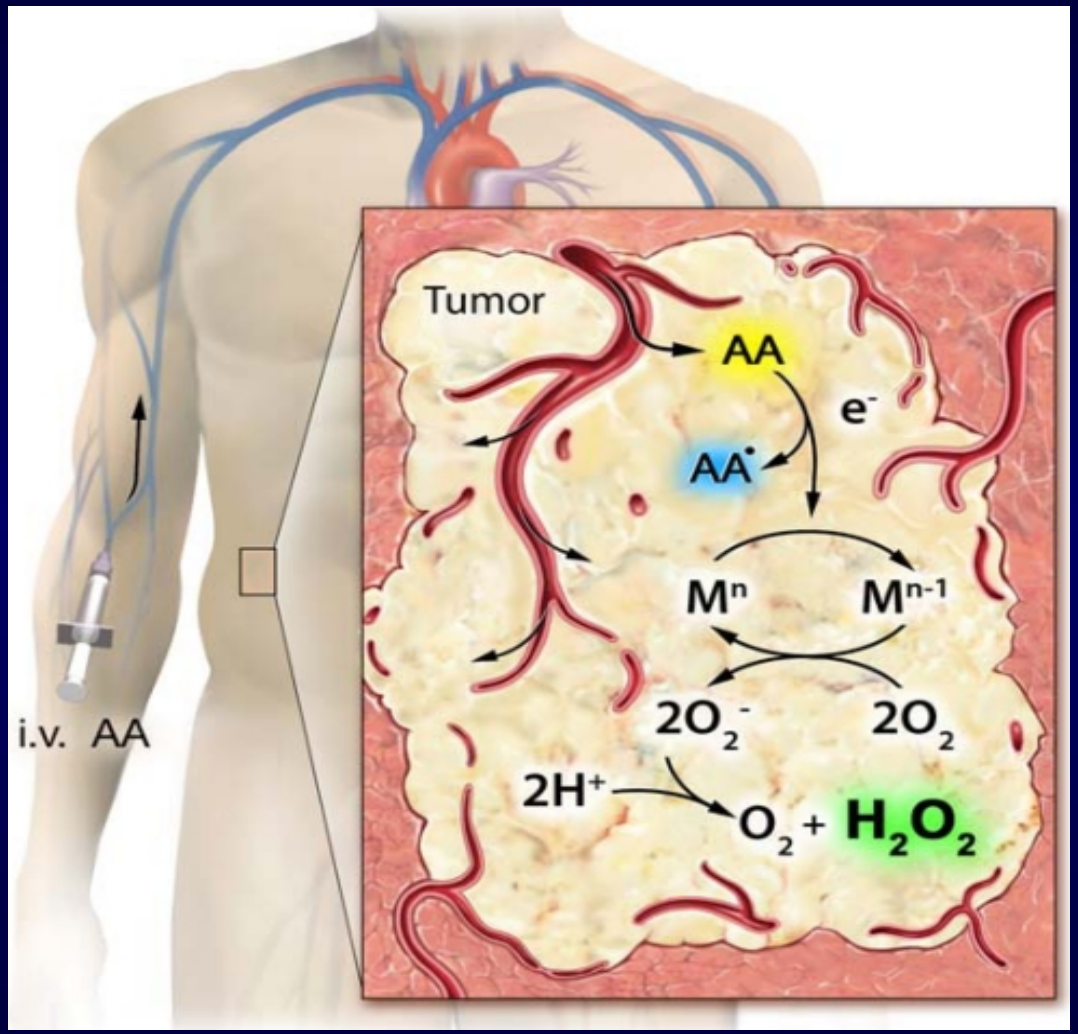
Effect of pharmacological levels of AA on implanted tumors



Pharmacological AA reduces growth of implanted tumors

Chen et al., PNAS; 2008 Aug 12;105(32):11105-9.

Proposed mechanism of AA action on tumors



High dose AA perfuses interstitium of tumor.

This forms an ascorbate radical.

The AA radical interacts with a metalloprotein catalyst and forms…

A superoxide radical, which becomes…

Hydrogen peroxide, triggering apoptosis etc.

Reaction is minimized in blood.

AA acts as a prodrug delivering H2O2 in tumors

Chen et al., PNAS; 2008 Aug 12;105(32):11105-9.

Recent clinical studies on IV-C

Phase I trial: n=15, advanced solid tumors, 4 days/week for 4 weeks. Well tolerated. No objective antitumor response. Recommended dose: 70-80 gm/m^2.

Phase I trial: n=9, metastatic pancreatic cancer, 2 days/week with gemcitabine, designed to achieve plasma level of 350 mg/dl. No dose-limiting toxicities. Mean survival of pts completing 8 weeks or more: 13 m.

Phase I trial: n=14, metastatic pancreatic cancer, 3 days/week with gemcitabine and erlotinib standard regimens. No serious toxicities related to IV-C. 7 of 9 subjects had stable disease.

Phase I trials indicated high-dose IV-C can be given safely in conjunction with chemotherapy regimens. Results suggest possible tumor response when given with chemotherapy.

Stephenson, Cancer Chemother Pharm. 2013: 72:139-46; Welsh, Cancer Chemother Pharm 2013; 71: 765-75; Monti, PLoS One 2012; 7:e29794.

IV Glutathione and chemotherapy

Exogenous glutathione and cytotoxicity in ovarian cancer:

Two ovarian cancer cell lines, A2780 and IGROV-1.

Glutathione administered to both:

A2780: IC50 = 0.23 mM for cytotoxicity

IGROV-1: no cytotoxic effect with Glutathione

Glutathione caused increase in H202 in cancer cells, measured by phenol red assay.

H202 give with glutathione caused apoptosis in A2780 but not IGROV-1 cells; IGROV-1 cells had higher levels of anti-apoptotic Bcl-2.

1.5 g glutathione in adult with 5 liters blood gives blood level of 0.64 mM, higher than IC50.

IV glutathione appears to have a prooxidant effect in cancer cells.

Perego, 2000; Int J Cancer 2000; 87:343-8; Dettman, ACNEM Journal. 2012 Mar. 31(1):8-11.

Glutathione Studies

- Majority were platinum-based tx's, primarily looking at reduction of toxicity.
- All the GSH studies had the same or lower incidence of toxicities in the GSH group versus the control group.

Reference	Patients and cancer type	GSH dose (over 15 min,)	Responses in GSH group vs. control	Toxicity in GSH group vs. control
Cascinu et al, 1995	n=50 Advanced gastric	1500 mg/m^2	76% vs. 52% CR+PR	17% vs. 89% neurotoxicity (p=0.0001)
Cascinu et al, 2002	n=52 Advanced colorectal	1500 mg/m^2	27% vs 23% CR+PR	0% vs 26% grades 3-4 neurotoxicity (p=0.01)
Smyth et al, 1997	n=151 Ovarian (I-IV)	3000 mg/m^2	73% vs 62% CR+PR	58% vs 39% completed 6 cycles chemo (p=0.04)
Schmidiger et al, 2002	n=20 Lung, H/N	5000 mg/m2	55% vs 50% CR+PR	Reduced hemotoxicity; (p=0.04-0.004)
Bogliun et al, 1996	n=54 Ovarian	2500 mg/m2	70% vs 59% CR+PR	26% vs 50% neurotoxicity
Colombo et al, 1995	n=33 Ovarian	2500 mg/m2	CR 44% vs 27% Survival 21 vs 16m	13% vs 27% neuropathy
Fujimoto et al, 1938	n=207 Gastric	30 mg/m2	Similar survival	Similar toxicity
Milla et al, 2009	n=27 Coloretal	1500 mg/m2	Similar platium-DNA adduct formation	Less neuropathy, p=0.0037

Prooxidant mechanisms of antioxidants in cancer : summary

1. Antioxidants appear to interact with copper ions in cancer cells, producing ROS promoting apoptosis

2. High doses of antioxidants appear to produce ROS (or have other effects) that encourages apoptosis in cancer cells. This may explain reports of synergisms with chemotherapy in vivo and clinically.

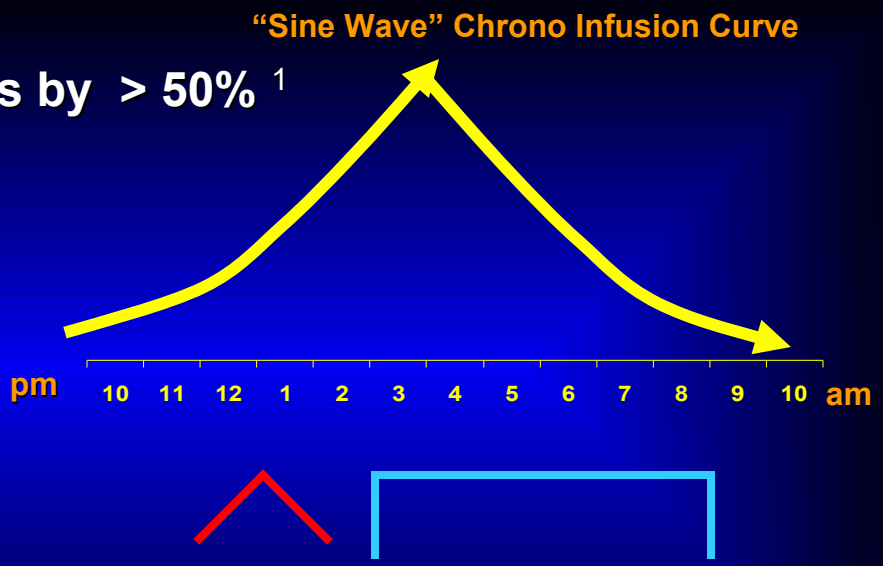
3. High-dose IV-C produces H202 in cancer cells through the interaction with metalloprotein enzymes; this may improve cytotoxicity of chemotherapy.

4. High-dose glutathione produces H202 in cancer cells, promoting cytotoxicity at a level that is consistent with normal IV doses.

5. The effect of antioxidants on cancer cells, is generally not similar as that of normal cells.

CHRONOMODULATED CHEMO ADMINISTRATION

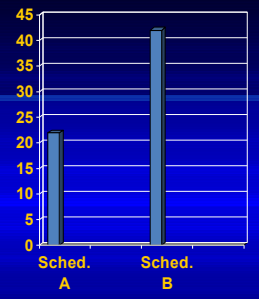
- Reduces toxicity – cuts adverse effects by > 50% [1]
- Improve treatment response
- Improve outcome
- Can rechallenge with prior chemo

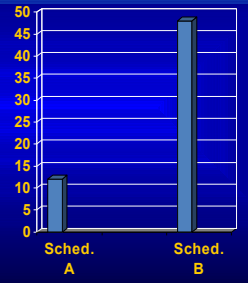


Example: **Metastatic Ovarian Cancer Trial**

RCT, Optimal timing vs inverted timing (Cis-Plat/Dox)

- 50% reduction in complications
- 80% reduction in need to reduce dosage





- Four-fold improvement in 5-yr survival (44% vs 11%)

Colon Cancer With Liver Mets

RL, Metastatic Colon cancer 1998

5-FU, LCV → severe vomiting
11/99 liver mets; resected

1/00 Block Center: began Integ regimen
Continuous infusion
5FU, LCV, CPT-11 → severe vomiting

Chronotherapy infusion
2/00 Same regimen, → no complaints

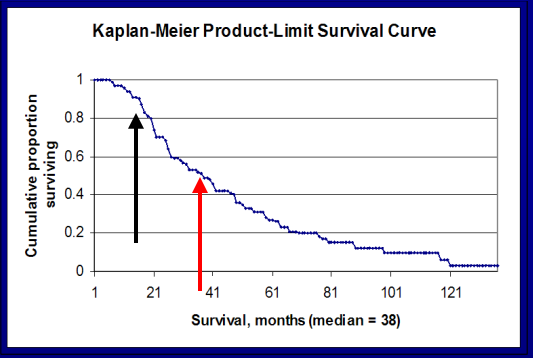
6/00 Update CT scans clear

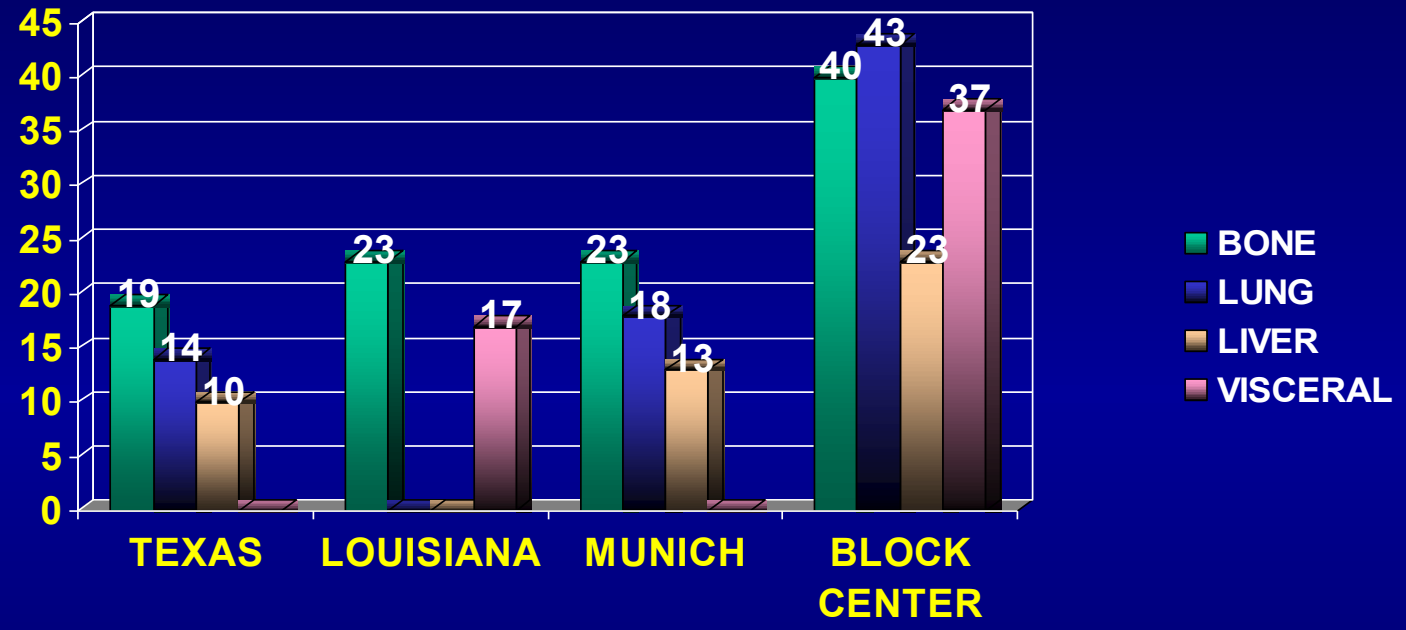
3/11 - Alive, well and remains free of disease at 14 years

Metastatic Breast Cancer Patients
Longitudinal Consecutive Cohort at Block Center
Block et al, Breast Journal July-Aug 2009

Median survival, months

N=90; Stage IV relapsed patients.





Whole system integrative treatment, chemotherapy combined with aggressive antioxidant therapy[1]

90 Advanced Met Breast Cancer: Median survival - 38 mo's vs 18 mo's

27 Advanced Met Prostate Cancer: Median survival - 61 mo's vs 23 mos

Metastatic Breast Cancer 1999
w/ Liver Mets

4/99 – Ductal Ca 4/10 + nodes,
Stage II ER- PR- H2N+

6/00 - Liver Mets

Began Block Center Program 2000

Alive & Well & Free of Disease

2012