National Institutes of Health
OFFICE OF DIETARY SUPPLEMENTS

CONFERENCE

January 14-15, 2003

Dietary Supplement Use in the Elderly

Should Breast Cancer Patients Taking Tamoxifen Consume Soyfoods?

Mark Messina

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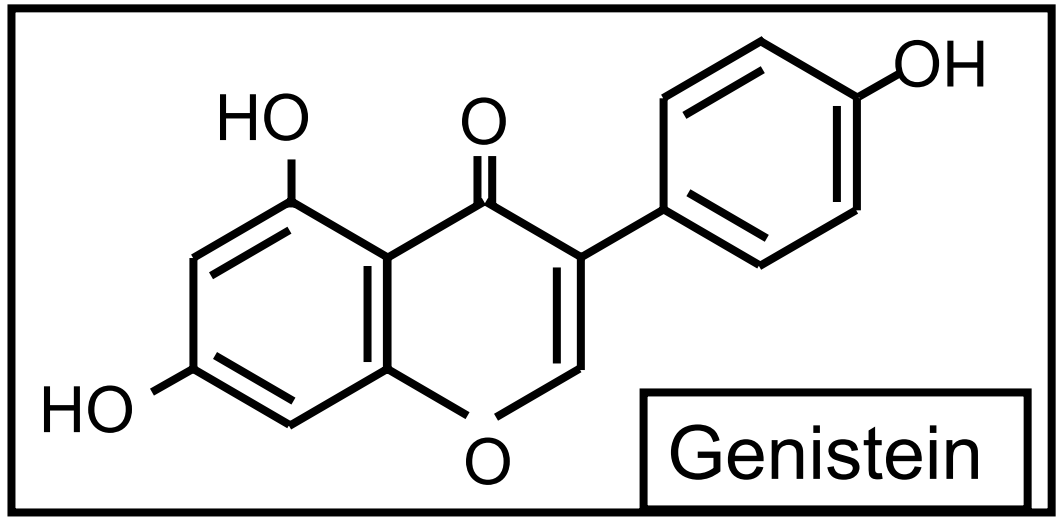
Hypothesis:
Early Soy
Intake ↓ Adult
BCa Risk

- Migration data
- Animal data
- Epidemiologic data

Isoflavone Isomers



Glycoside (+ glucose)

- Genistin
- Daidzin
- Glycitin

Aglycone (- glucose)

- Genistein
- Daidzein
- Glycitein

Intestinalm icroflora

Equol

30-50% of subjects

Possible Mechanisms for the Biological Effects of Isoflavones

- Hormonal
  - Estrogen-like
  - Antiestrogenic
- Nonhormonal
  - Signal transduction
  - Antioxidant effects
  - Antiangiogenesis

Selective Estrogen Receptor Modulators

Genistein: Does It Prevent or Promote Breast Cancer?

Kerrie B. Bouker and Leena Hilakivi-Clarke

Environ Health Perspect 108: 701, 2000

Department of Oncology, Lombardi Cancer Center, Georgetown University, Washington, DC, USA

"… studies indicating a cancer-promoting effect of genistein should not be taken lightly."

American Institute for Cancer Research 11th Annual Research Conference on Diet, Nutrition and Cancer

Soy for Breast Cancer Survivors: A Critical Review of the Literature[1]

Mark J. Messina[2] and Charles L. Loprinzi*[3]

131: 3095S, 2001

"... If women (with or without breast cancer) enjoy partaking of soy products, then it seems quite reasonable for them to partake of them."

THE JOURNAL OF NUTRITION
November 2001 Volume 131 No. 11S ISSN 0022-3166

COMPLEMENTARY AND ALTERNATIVE MEDICINE SERIES
Series Editors: David M. Eisenberg, MD, and Ted J. Kaptchuk, OMD

ACADEMIA AND CLINIC

Advising Patients Who Seek Complementary and Alternative Medical Therapies for Cancer

Wendy A. Weiger, MD, PhD; Michael Smith, MR PharmS, ND; Heather Boon, BScPhm, PhD; Mary Ann Richardson, DrPH; Ted J. Kaptchuk, OMD; and David M. Eisenberg, MD

"… women taking tamoxifen should especially avoid soy supplements."

Ann Intern Med 137: 889, 2002

"These results raise concern about consuming dietary isoflavone supplements in conjunction with tamoxifen in postmenopausal women who have estrogen dependent breast cancer …"

William Helferich, PhD
University of Illinois

Relative Binding Affinities of Selected Compounds

	RBA	
Compound	ERα	ERβ
17β-estradiol	100	100
Tamoxifen	4	3
4-OH-tamoxifen	257	237
Genistein	4	87
Daidzein	0.1	0.5

RBA by solid-phase (Scintistrip) competition, =the ratio of concentrations of 17β-E2 & competitor required to reduce the specific radioligand binding by 50% with the RBA for 17β-E2 arbitrarily set at 100. Endocrinol 139: 4252, 1998

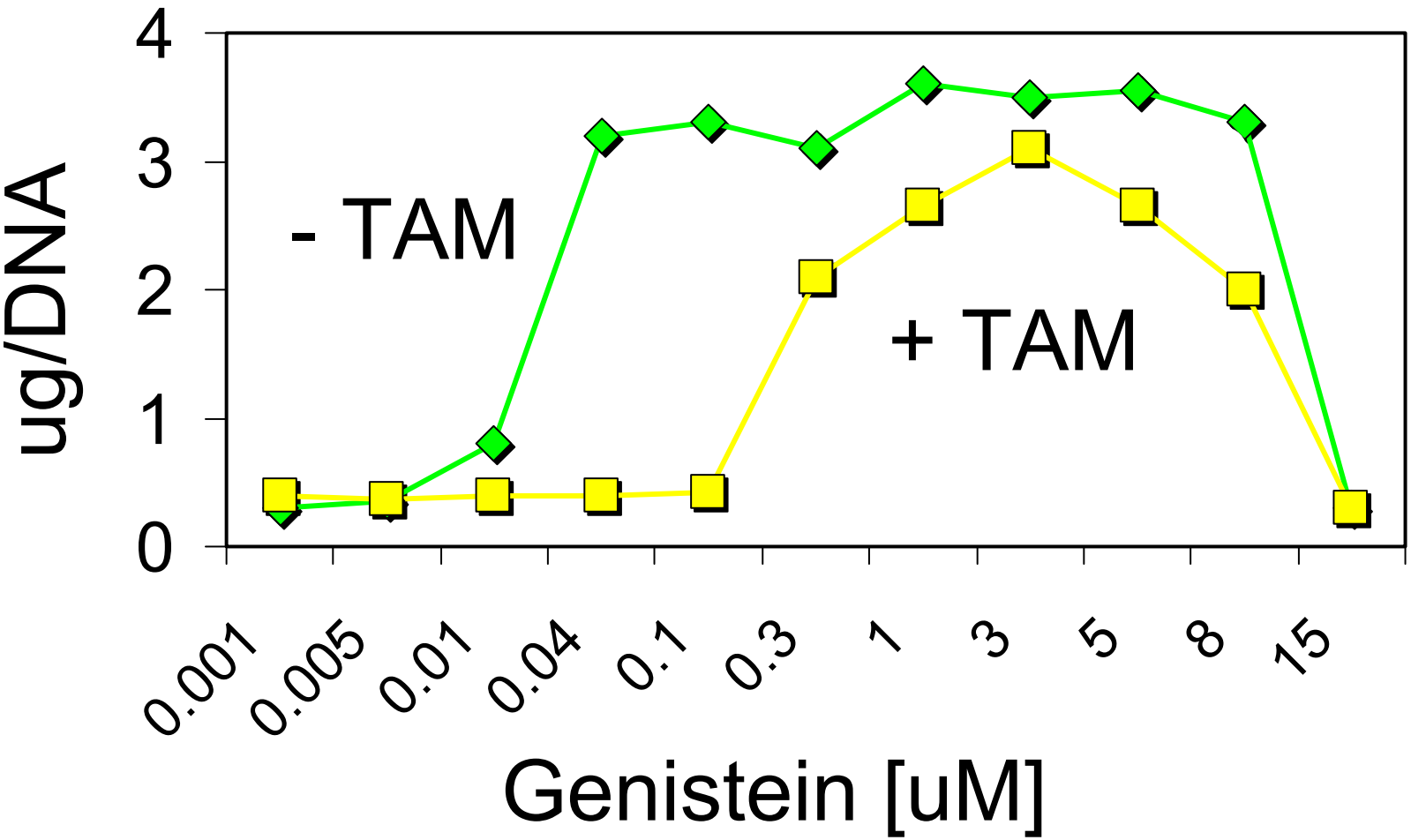
In Vitro Effects of Tamoxifen (TAM) on Isoflavones (IFs)

- TAM & IFs compete for binding to estrogen receptors
- TAM inhibits the “estrogenic” effects of low [IFs] on BCa cells
- No (-) effects of TAM on the growth inhibitory effects of high [genistein]
- TAM sensitized T47D (ER+) cells to the inhibitory effects of genistein

Isoflavone Pharmacokinetics

- Absorption, ≈ 30- 50%
- Half-life, 6-9 hours
- Peak serum levels, 6 hours
- Free living Japanese adults fasting levels, 200-500 nM
- Clinical studies, 1- 5 uM
- Mostly conjugates in serum

Effect of Genistein on T47D (ER+) BCa Cells +/- Tamoxifen

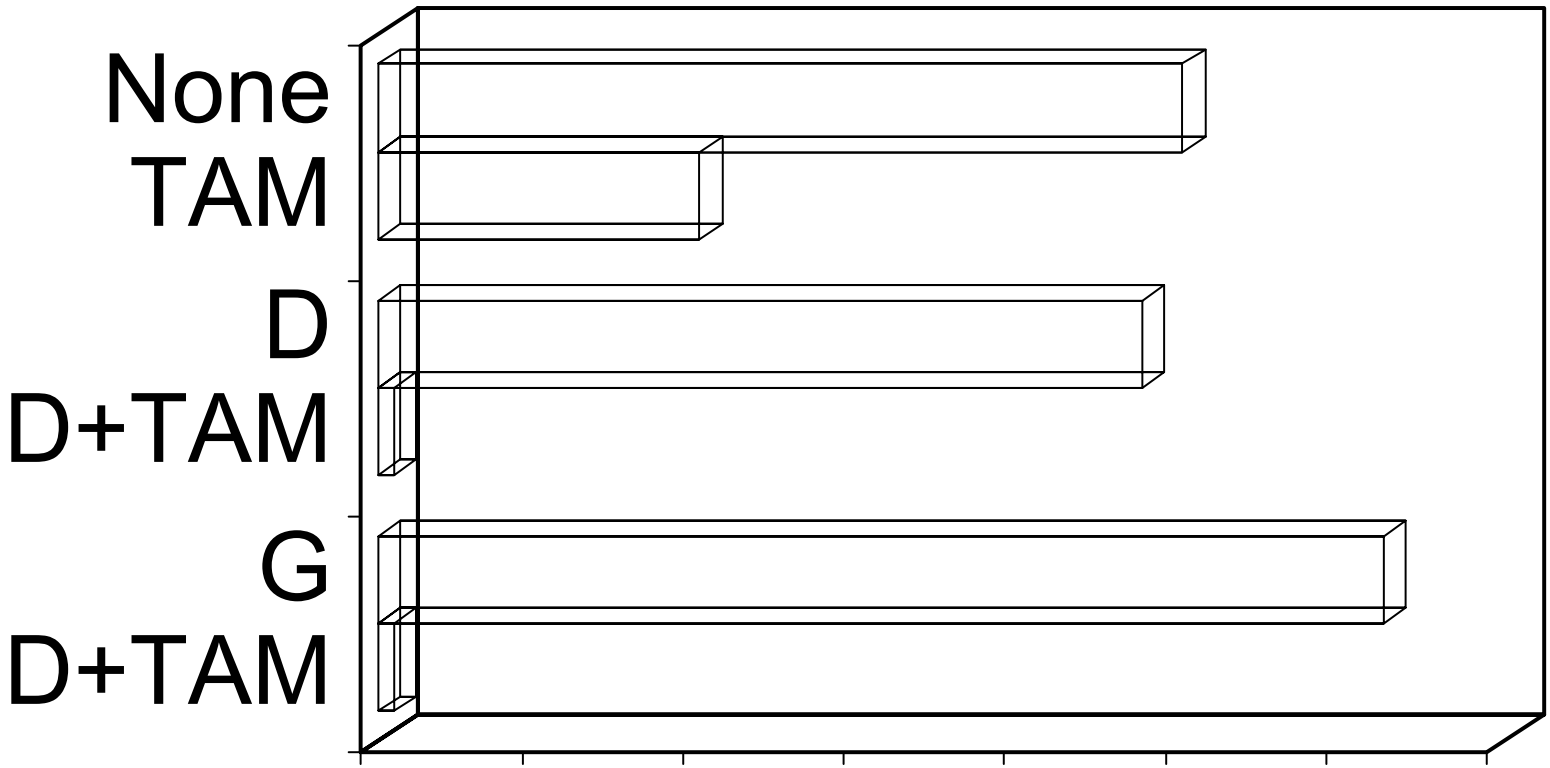


In Vitro Effects in T47-D (ER+) Breast Cancer Cells in a Low Estrogen Environment

	% Proliferation
Control	100.0
Tamoxifen [1 uM]	92.8*
Genistein [1 uM]	100.0
TAM + GEN	96.7

* P < 0.05 vs control; Am Surgeon 68: 575, 2002

Effects of TAMoxifen, Daidzein, & Genistein Alone & in Combination on MCF-7 Cell Growth



In Vitro Cell Dev Biol 37: 275, 2001 (medium includes 1 uM environmental estrogens)

Relative cell number (%)

Antiproliferative Action of Tamoxifen & Genistein in MDA-MB-435 (ER-) BCa Cells

Tamoxifen [uM]	Genistein [uM]	% of control
5	0	91
0	5	82
5	5	44*

Statistically significant interaction; Anticancer Res 19: 1657, 1999

In Vitro Effects of Genistein and Tamoxifen on 6 Different Types of Breast Cells

- Genistein dose-dependently (4-40 uM) inhibits the growth of ER+ dysplastic & ER+/- malignant cells
- Adding tamoxifen (1-10 uM) leads to a synergistic inhibition of dysplastic cells and an additive inhibitory effect on malignant cells

Eur J Obstetrics Gynecol Reproductive Biol 102: 188, 2002

Effects of TAM & GEN on MCF-7 Cell Growth in OVX Athymic Mice

Group	Tumor (mm^2)
Control	5.9
Estrogen (E2)	116.5
E2 + TAM	14.4
E2 + TAM + GEN	75.1

CR 62: 2474, 2002; 32 wks, ovx mice, TAM mg, Gen, 1000 ppm; serum, 4-5 uM.

Effects on DMBA-Induced Rat Mammary Cancer

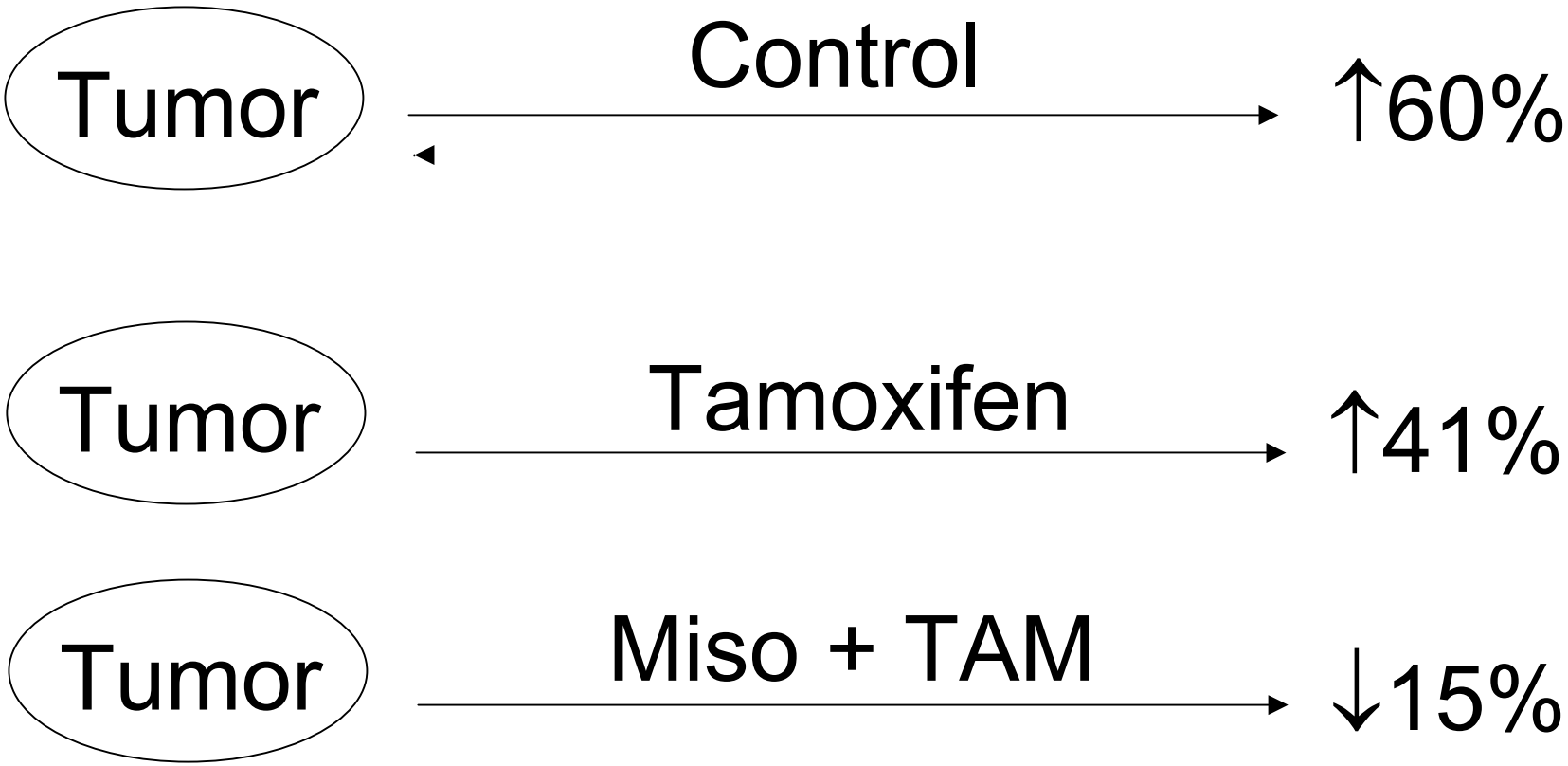
Group	Tumors/rat
Control	7.6
Tamoxifen	5.9 (29% ↓)
Soy	5.0 (37% ↓)
Soy + TAM	3.0 (62% ↓)*

Effects of Miso & Tamoxifen on MNU Rat Mammary Cancer

Group	Incidence (%)	Tumors per rat
Control	91	4.5*
Miso (10%)	77	2.4*
Tamoxifen	68	1.4*
Miso+TAM	10	0.2*

Jap J Cancer Res 89: 487, 1998

Mammary Tumor Size 6 Weeks after Start of Treatment



Tumor initiation, MNU; TX iniated after tumors reached 10-25 mm; Jpn J CR 89: 487, 1998

American Society of Clinical Oncology Breast Cancer Technology Assessment Working Group

"Use of tamoxifen in combination with hormone replacement therapy is not recommended outside of a clinical trial."

J Clinical Oncology 20: 3328, 2002

Combined Effects of Tamoxifen and HRT on Breast Cancer Risk

- IBIS-1, N=7410 (OR = 0.67)
  - 1484 combined users - NI
- Royal Marsden N=2494 (OR = 0.83)
  - 523 combined users - NI
- Italian Study N=5408 (OR = 0.76)
  - ↓ risk only in combined users

Insights from the HRT Data

Observations	EPT	ET
Epi data: BCa risk	↑↑	↑
Cell proliferation	↑↑	↑
Breast tissue density	↑↑	↑
WHI	↑	---
Soy has no progestin activity		

Conclusions & Recommendations

- Theoretical basis for avoiding soy while on tamoxifen
- In vitro and animal data: both harmful & beneficial interactions
- Overall, data point toward beneficial effects
- Human studies need to be undertaken immediately