Krebsprävention- Antioxidantien, Selen und Jod

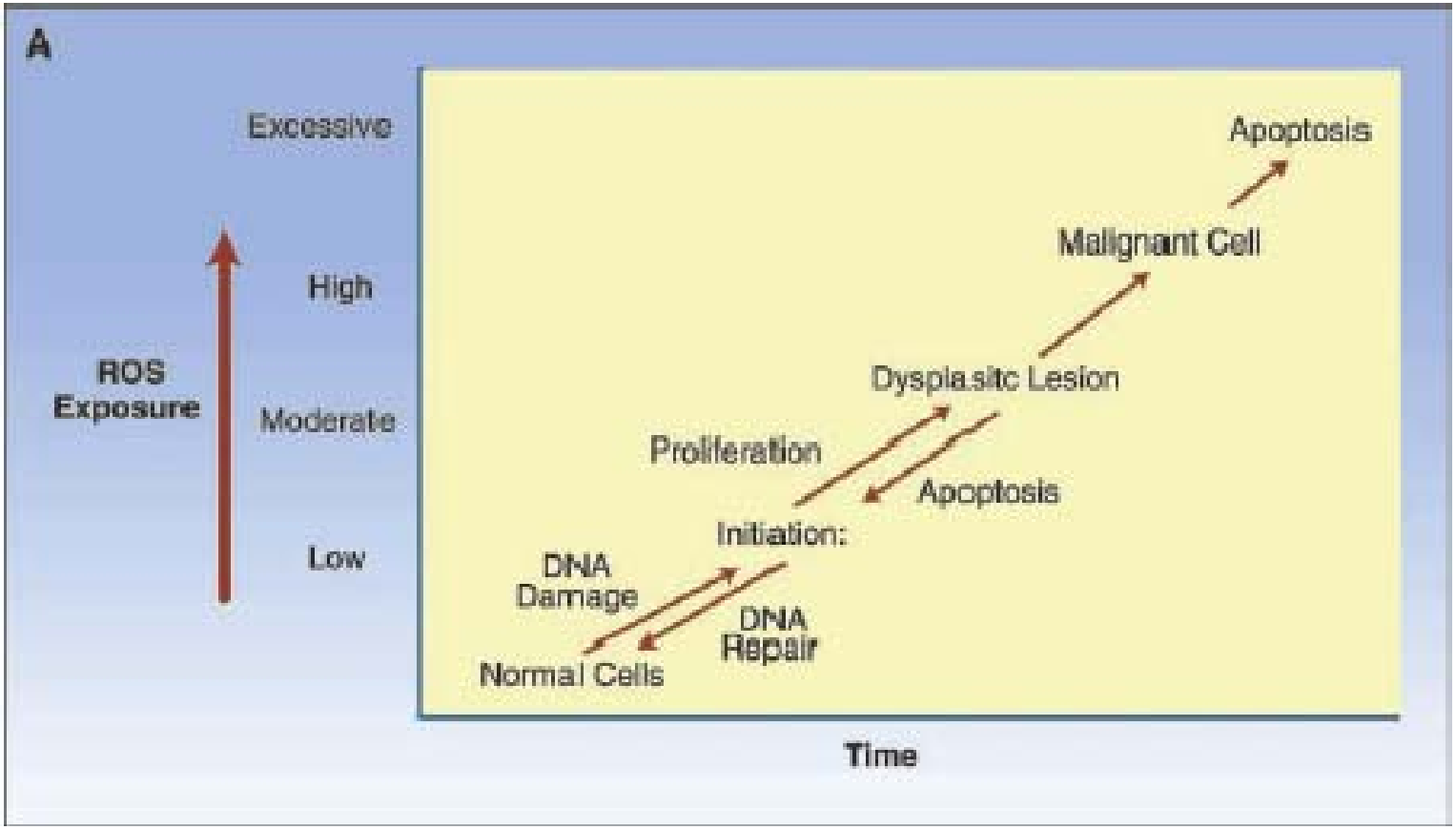
Roland Gärtner

Medizinische Klinik Innenstadt

MEDIZINISCHE KLINIK INNENSTADT

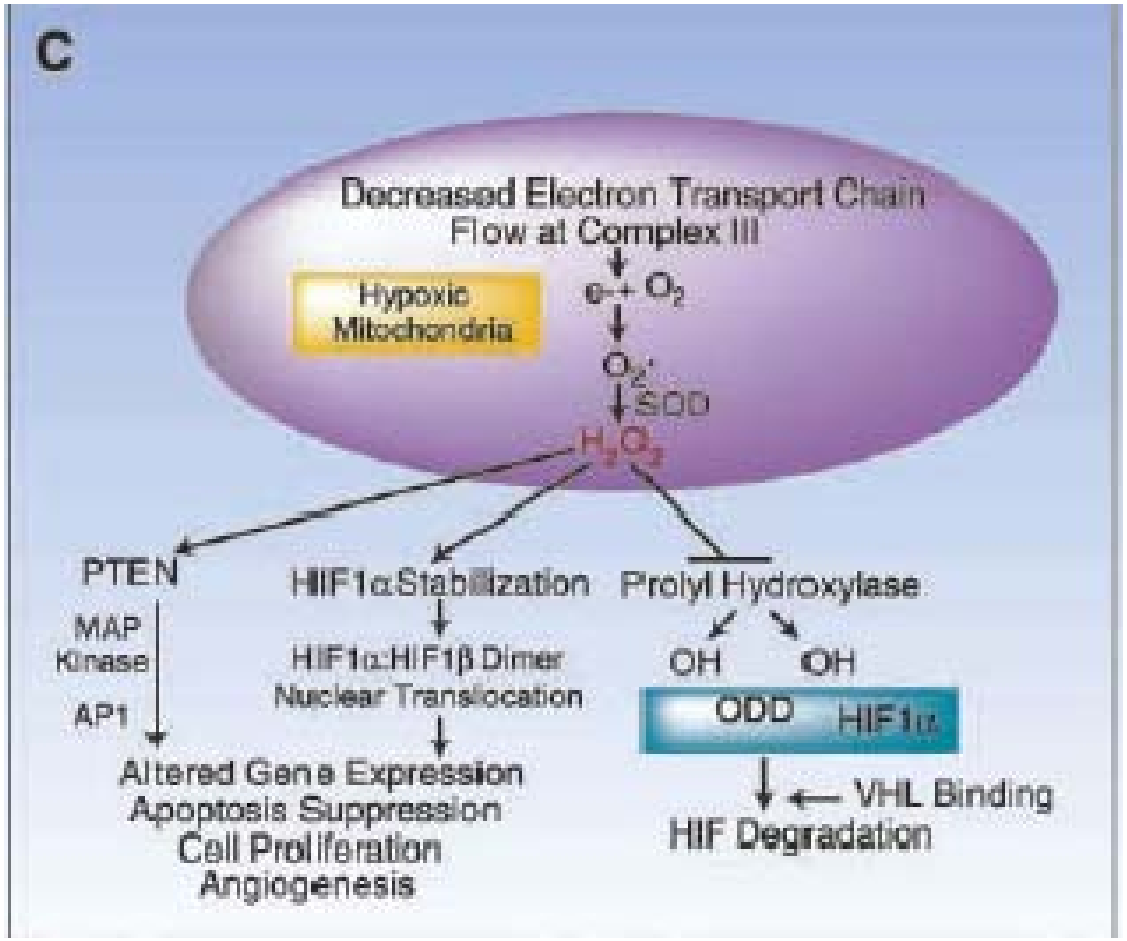
Klinikum der Universität München

Antioxidantien und Krebs



Clin Cancer Res 2007;13(3) February 1, 2007

Antioxidantien und Krebs



Clin Cancer Res 2007;13(3) February 1, 2007

Antioxidantien und Krebs

- Experimentelle und epidemiologische Untersuchungen ließen vermuten, dass eine höhere Dosen als normalerweise mit der Nahrung aufgenommene Antioxidantien Krebs verhindern können (Schrauzer 1977, Peto 1981, Willcox 2004)
- Zahlreiche Interventionsstudien wurden daher durchgeführt mit dem Ziel den Effekt einer zusätzlichen Supplementation mit antioxidativen Vitaminen zu untersuchen
- Gastrointestinale Karzinome sind mit am häufigsten (Garcea 2003, Sharma 2004, Grau 2006)

Antioxidant supplements for preventing gastrointestinal cancers (Review)

Bjelakovic G, Nikolova D, Simonetti RG, Gluud C

Antioxidant supplements	RDA*		TUIL**	Experimental doses	Regimen
	Man	Woman			
Beta-carotene	ND		ND	6 to 30 mg	Daily or on alterrate days
Vitamin A	900 µg	700 µg	3000 µg	1500 to 15000 µg	Daily
Vitamin C	90 mg	70 mg	2000 mg	120 tc 2000 mg	Daily
Vitamin E	15 mg	15 mg	1000 mg†	30 to 600 mg	Daily or on alterrate days
Selenium	55 µg	55 µg	400 µg	50 to 228 µg	Daily

ND – not determined

Cochrane Collaboration 2008

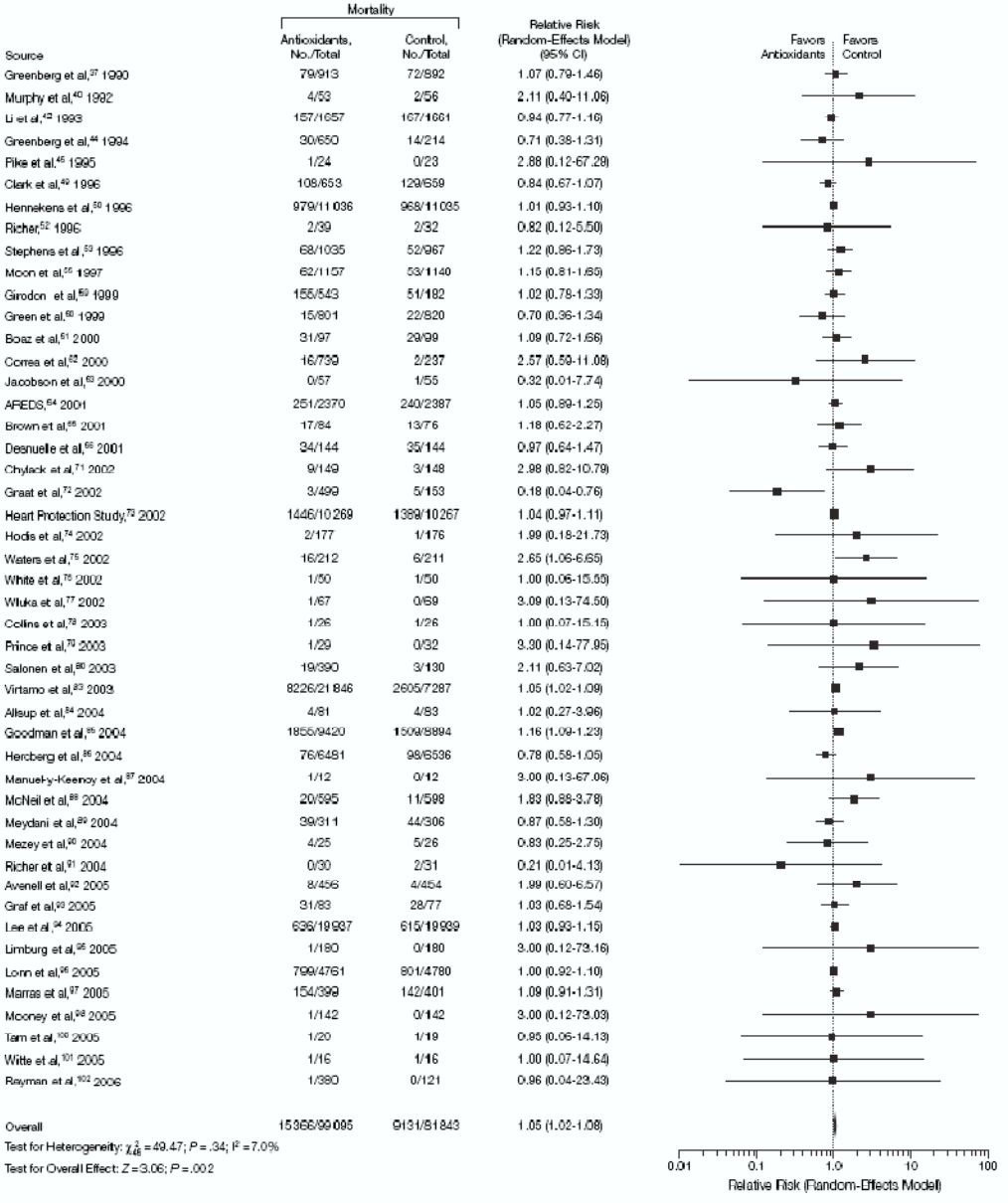
Experimental antioxidant supplements	Oesophageal cancer	Gastric cancer	Colorectal cancer	Pancreatic cancer	Hepatocellular carcinoma
Beta-carotene (PHS 1996; Correa 2000; ATBC 2003; Zhu 2003)	0.75, 0.25 to 2.30	1.12, 0.79 to 1.59	1.09, 0.79 to 1.51	1.02, 0.54 to 1.90	1.92, 0.96 to 3.85
Vitamin E (ATBC 2003; HOPE TOO 2005)	1.46, 0.72 to 2.96	1.30, 0.90 to 1.88	1.10, 0.87 to 1.39	0.97, 0.67 to 1.39	1.33, 0.63 to 2.82
Selenium (Yu 1991; NPCT 1996; Yu 1997; Li 2000; Li 2004)	0.40, 0.08 to 2.07	0.76, 0.44 to 1.31	0.48, 0.22 to 1.05	ND	0.56, 0.42 to 0.76
Beta-carotene and vitamin A (CARET 2004)	1.43, 0.90 to 2.29	0.89, 0.46 to 1.73	0.97, 0.76 to 1.25	1.33, 0.84 to 2.09	1.35, 0.51 to 3.54
Beta-carotene and vitamin C (Correa 2000)	ND	2.90, 0.12 to 70.52	ND	ND	ND
Beta-carotene and vitamin E (ATBC 2003)	1.23, 0.59 to 2.56	1.40, 0.98 to 2.01	1.20, 0.89 to 1.63	0.93, 0.65 to 1.35	1.25, 0.59 to 2.67
Beta-carotene, vitamin C, and vitamin E (HPS 2002; Plummer	1.19, 0.71 to 2.01	1.25, 0.78 to 2.00	0.84, 0.65 to 1.07	1.00, 0.57 to 1.76	1.40, 0.44 to 4.41

Experimental antioxidant supplements	Oesophageal cancer	Gastric cancer	Colorectal cancer	Pancreatic cancer	Hepatocellular carcinoma
Vitamin A, riboflavin, and zinc (Munoz 1985)	1.33, 0.30 to 5.91	ND	ND	ND	ND
Vitamin C, vitamin E, and selenium (SIT 2006)	ND	1.01, 0.60 to 1.68	ND	ND	ND
Beta-carotene, vitamin C, vitamin E, and selenium (SUVIMAX 2004)	1.01, 0.14 to 7.16	1.01, 0.14 to 7.16	0.88, 0.49 to 1.58	0.67, 0.19 to 2.38	1.01, 0.06 to 16.12
26 vitamins/minerals (NIT2 1993)	0.96, 0.76 to 1.22	1.19, 0.89 to 1.58	ND	ND	ND

Bjelakowski et al.
Jama 2007

Bjelakowski et al.
Jama 2007

Figure 2. Intervention Effect of Antioxidant Supplements vs Placebo on Mortality in Trials With Low Risk of Bias



Conclusions Treatment with beta carotene, vitamin A, and vitamin E may increase mortality. The potential roles of vitamin C and selenium on mortality need further study.

Krebs-Prophylaxe mit Antioxidantien

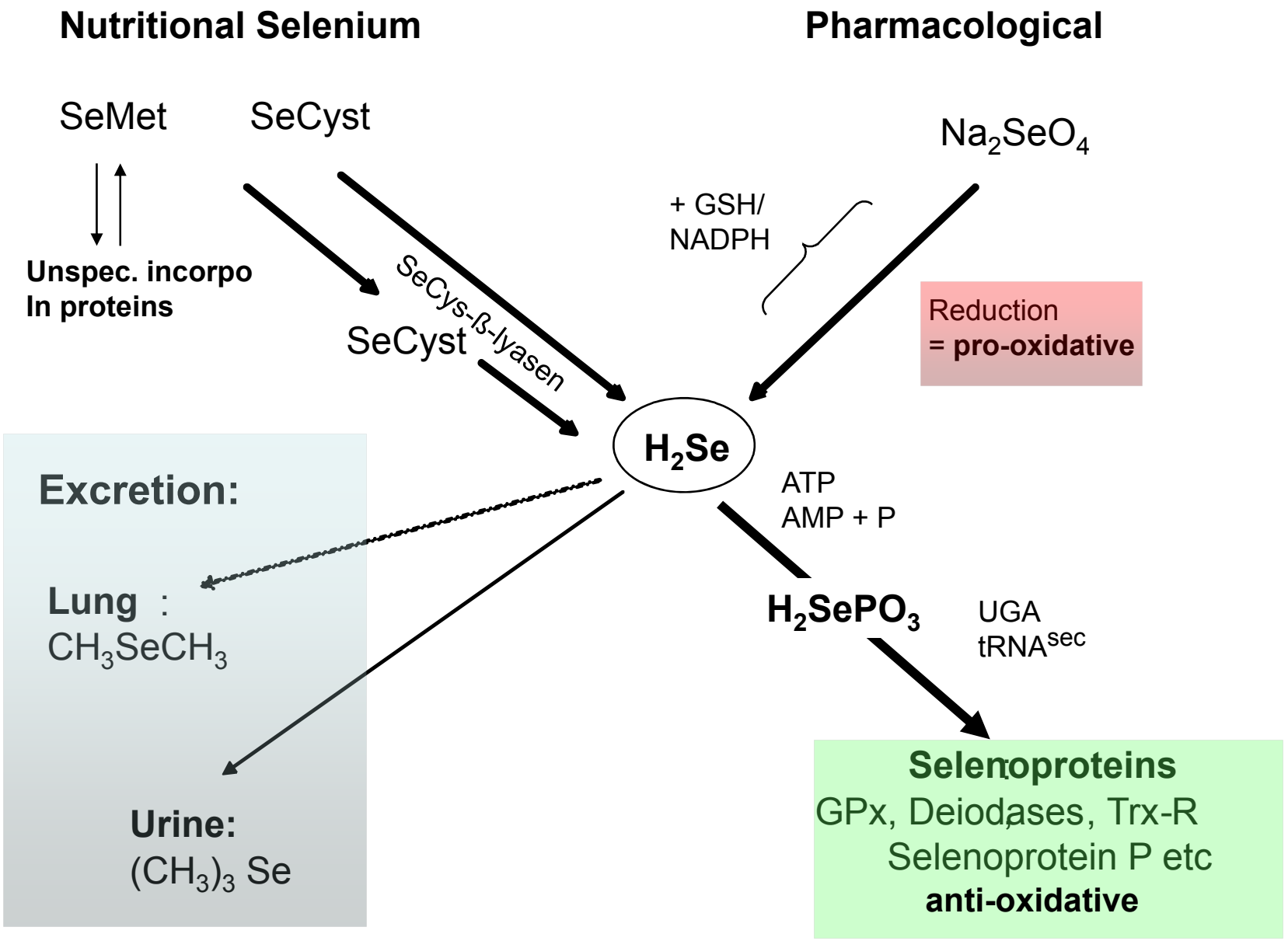
- Bisher gibt es trotz zahlreicher prospektiver, Placebo-kontrollierter Untersuchungen keinen Hinweis darauf, dass eine erhöhte Zufuhr von antioxitativ wirksamer Vitamine Karzinome verhindert werden können oder die Mortalität hierdurch beeinflusst werden kann.
- Hohe Dosen an ß-Carotin, Vitamin A oder E sind möglicherweise sogar schädlich

Antioxidantien

- Enzymatisch
  - Superoxyd-Dismutase
    - $O_2^- > H_2O_2$
  - Catalase
    - $H_2O_2 > H_2O + O_2$
  - Glutathionperoxidase
    - $GSH + H_2O_2 > GSSG + H_2O$

- Nicht-enzymatisch
  - Vitamin C
  - Vitamin E
  - Vitamin A/ß-Caroten
  - Glutathion
  - N-acetylcystein

Selenium metabolism



Gärtner J Lab Med 2006

Selen ist ein essentielles Spurenelement...

- **Selenocystein, die 21. genomische Aminosäure – steht im Zentrum einer Reihe von Enzymen, die für die Homöostase des zytosolischen, nukleären und plasmatischen Redoxsystemes verantwortlich sind**
- **Selenoenzyme modulieren Immunfunktion**

Selenoproteins – functions

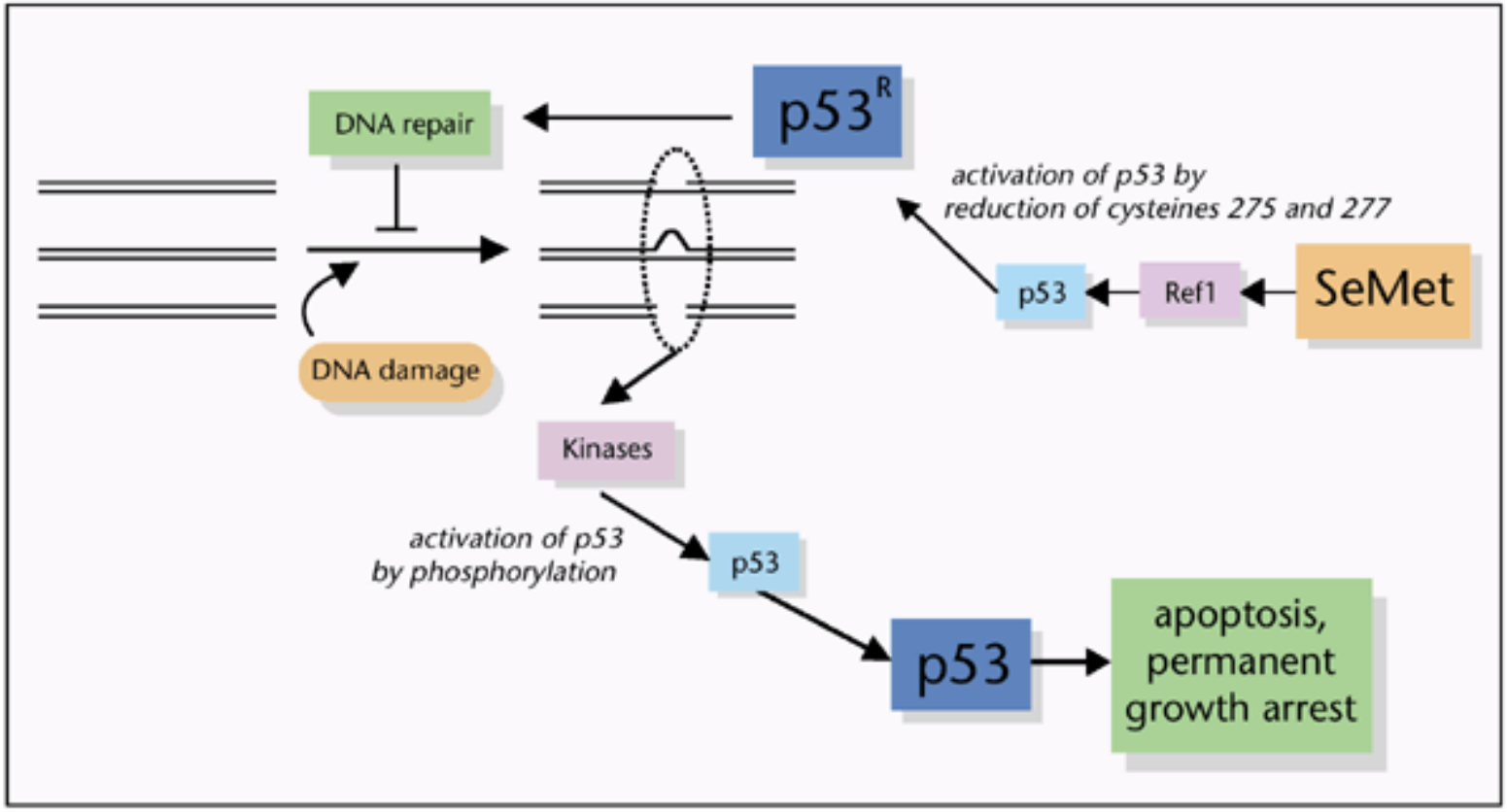
GPx Maintenance of the redox potential in plasma and cytosol

TrxR maintenance of redox potential in nucleus, regulation transcription factors i.e NFkB and Cytokine-expression

Selenoprotein P: transport of selenocystein prevents endothelium from peroxidation and activation

Selen kann Prostata-Karzinomzellen rediffernzieren

Seo, Y.R., Kelley, M., Smith, M L. Selenomethionine regulation of p53 by a ref-1-dependent redox mechanism. Proc. Natl. Acad. Sci. 2002



Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: an analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial

A.J. DUFFIELD-LILLICO, B.L. DALKIN*, M.E. REID†, B.W. TURNBULL‡, E.H. SLATE¶, E.T. JACOBS, J.R. MARSHALL† and L.C. CLARK, for the Nutritional Prevention of Cancer Study Group

*Arizona Cancer Center, and *Urology Section, Department of Surgery, Arizona Cancer Center, College of Medicine, University of Arizona, Tucson, AZ, †Cancer Prevention & Population Sciences, Roswell Park Cancer Institute, Buffalo, NY, ‡School of Operations Research and Industrial Engineering, Cornell University, Ithaca, NY and ¶Department of Biometry and Epidemiology, Medical University of South Carolina, Charleston, SC, USA*

Accepted for publication 30 January 2003

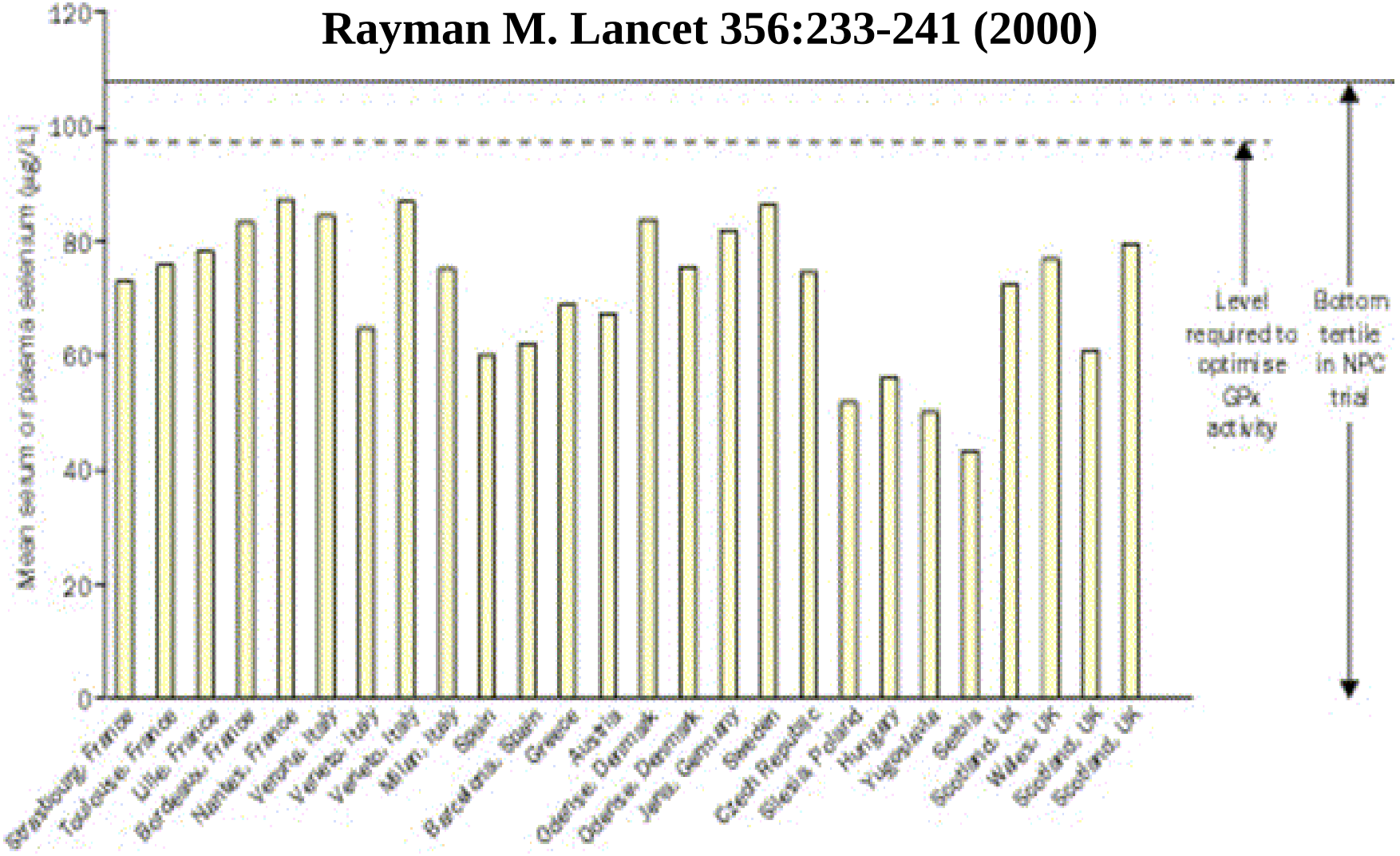
TABLE 2 Prostate cancer incidence by treatment group, follow-up period, baseline PSA and tertile of baseline plasma selenium

Group [n]	Cases, SS/placebo	Incidence† SS/placebo	Unadjusted RR (95% CI) [P]	Adjusted HR (95% CI) [P]
Follow-up				
1983–1993 [974]	13/35	–	0.37 (0.18–0.71) [0.002]*	0.35 (0.16–0.65) [0.001]†
1983–1996 [927]	22/42		0.51 (0.29–0.88) [0.009]*	0.48 (0.28–0.80) [0.005]†
Baseline PSA, ng/mL				
≤ 4 [624]	7/20	0.30/0.86	0.35 (0.13–0.87) [0.01]*	0.33 (0.14–0.79) [0.01]†
> 4 [70]	11/13	5.64/6.40	0.88 (0.36–2.13) [0.86, 0.13]†¶	0.95 (0.42–2.14) [0.90, 0.09]†§
Plasma selenium				
≤ 106.4 [317]	2/15	0.17/1.25	0.14 (0.02–0.59) [0.002]*	0.14 (0.03–0.61) [0.009]†
106.8–123.2 [305]	7/16	0.57/1.48	0.39 (0.14–0.99) [0.03]*	0.33 (0.13–0.82) [0.02]†
> 123.2 [305]	13/11	1.17/0.97	1.20 (0.50–2.97) [0.66,0.02]*¶	1.14 (0.51–2.59) [0.75,0.01]†§

**RR and †HR derived from incidence rate ratios, P from log-rank tests and Cox proportional hazard model adjusted for age (continuous) and smoking (never, former, current) at randomization; †Annual cumulative incidence per 100 PYs; P from log-rank test and ¶Mantel-Haenszel test for heterogeneity; §P for treatment group–characteristic interaction, for the (treatment group × factor) cross-product term in a Cox proportional hazards model.*

Mean Plasma Selenium levels in Europe, measured since 1990 and optimal level required for max GPx activity

Rayman M. Lancet 356:233-241 (2000)



Selen

- Eine Substitution mit 200 µg Selen/d scheint nach den bisherigen Untersuchungen die Inzidenz von HCC zu verhindern und auch Prostatkarzinome, besonders bei den Probanden mit den niedrigsten Selen-Plasma-Spiegeln

Derzeitige Studien zur Prävention von Prostata-Karzinom

Study type	Population	Sponsor	Agent	Sample size (approximate)	Estimated completion
General risk	Healthy	SWOG	Selenium & Vitamin E (SELECT)	32,400	2012
		Merck	Refocoxib	8000	Cancelled
		SWOG	Finasteride	19,000	Completed
Higher risk	Elevated PSA-negative biopsy	Glaxo Smith Kline	Dutasteride	8200	2010
Preneoplastic	High-grade prostatic intraepithelial neoplasia	GTX	Toremifene	1200	2010
		SWOG	Selenium	700	2011
		NCIC	Soy, Vitamin E, selenium	325	2008

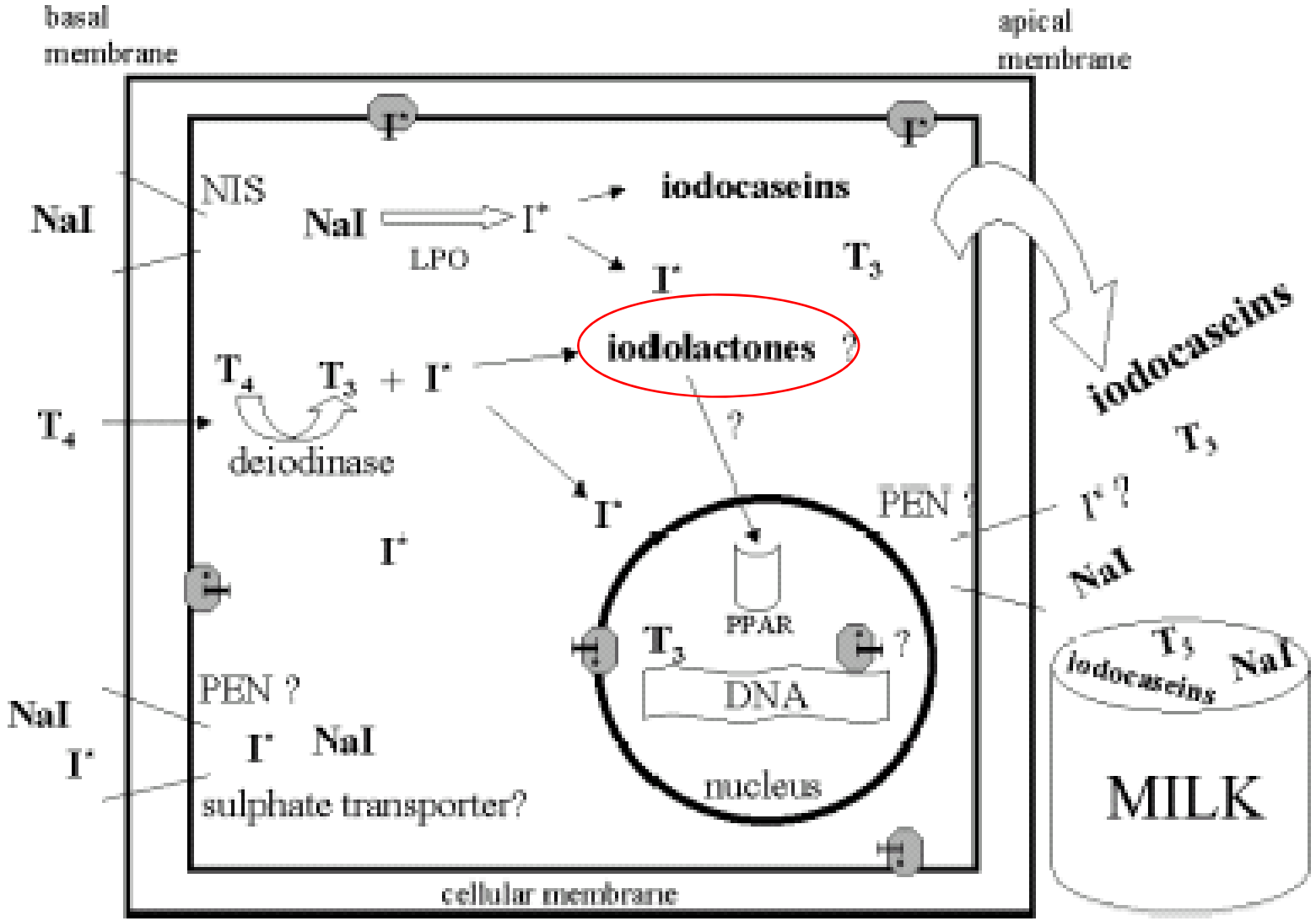
SWOG indicates Southwest Oncology Group; NCIC, National Cancer Institute of Canada.

Jod und Brustkrebs

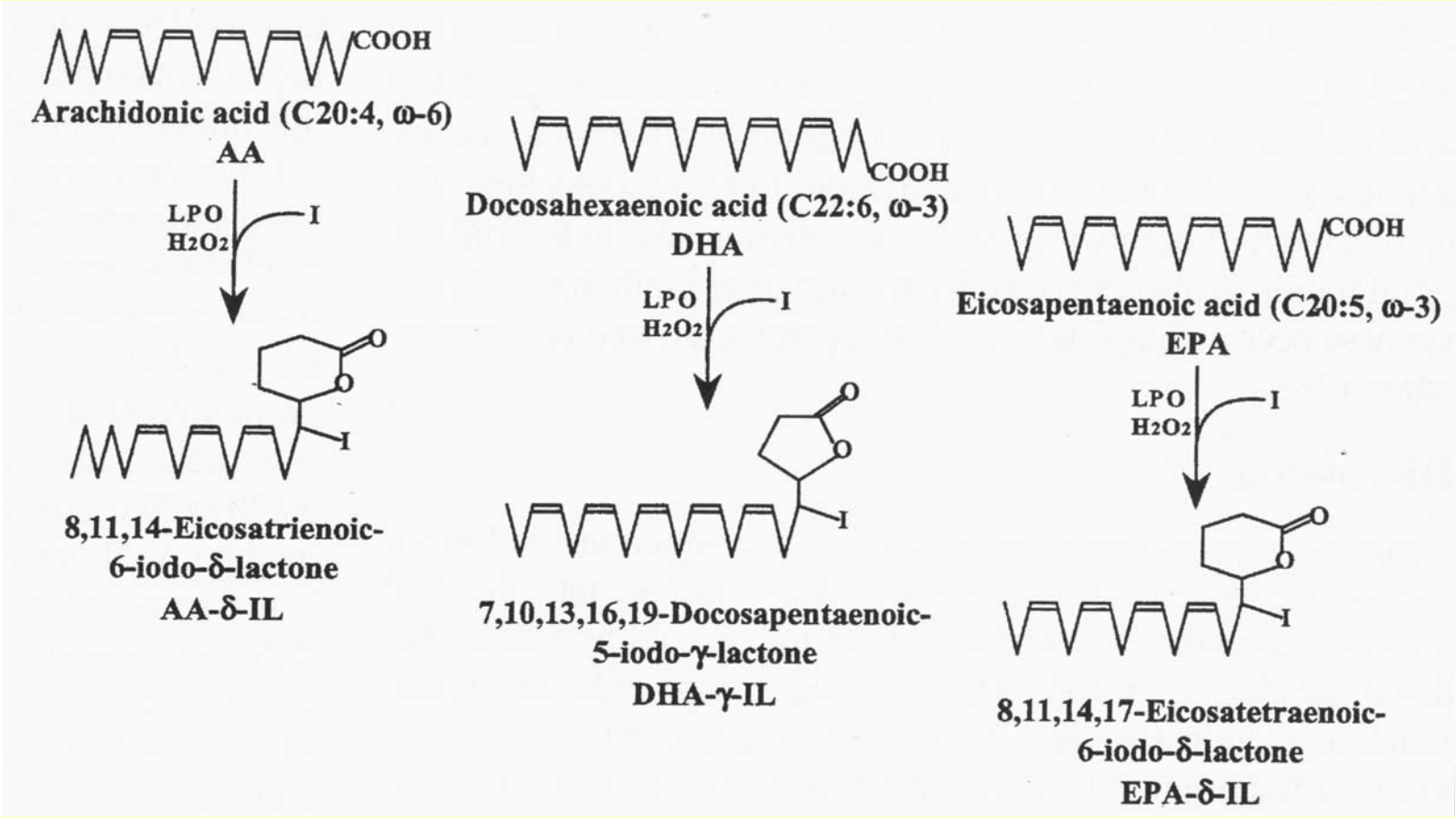
- Mammagewebe exprimiert NIS
- Brustkrebs 5-mal seltener in Gegenden mit hoher Jodzufuhr (Japan vs Europa)
- Algenextrakt verhindert experimentellen Brustkrebs bei Kaninchen und Ratten

Carmen Aceves,[1,2] Brenda Anguiano,[1] and Guadalupe Delgado[1]

Is Iodine A Gatekeeper of the Integrity of the Mammary Gland?

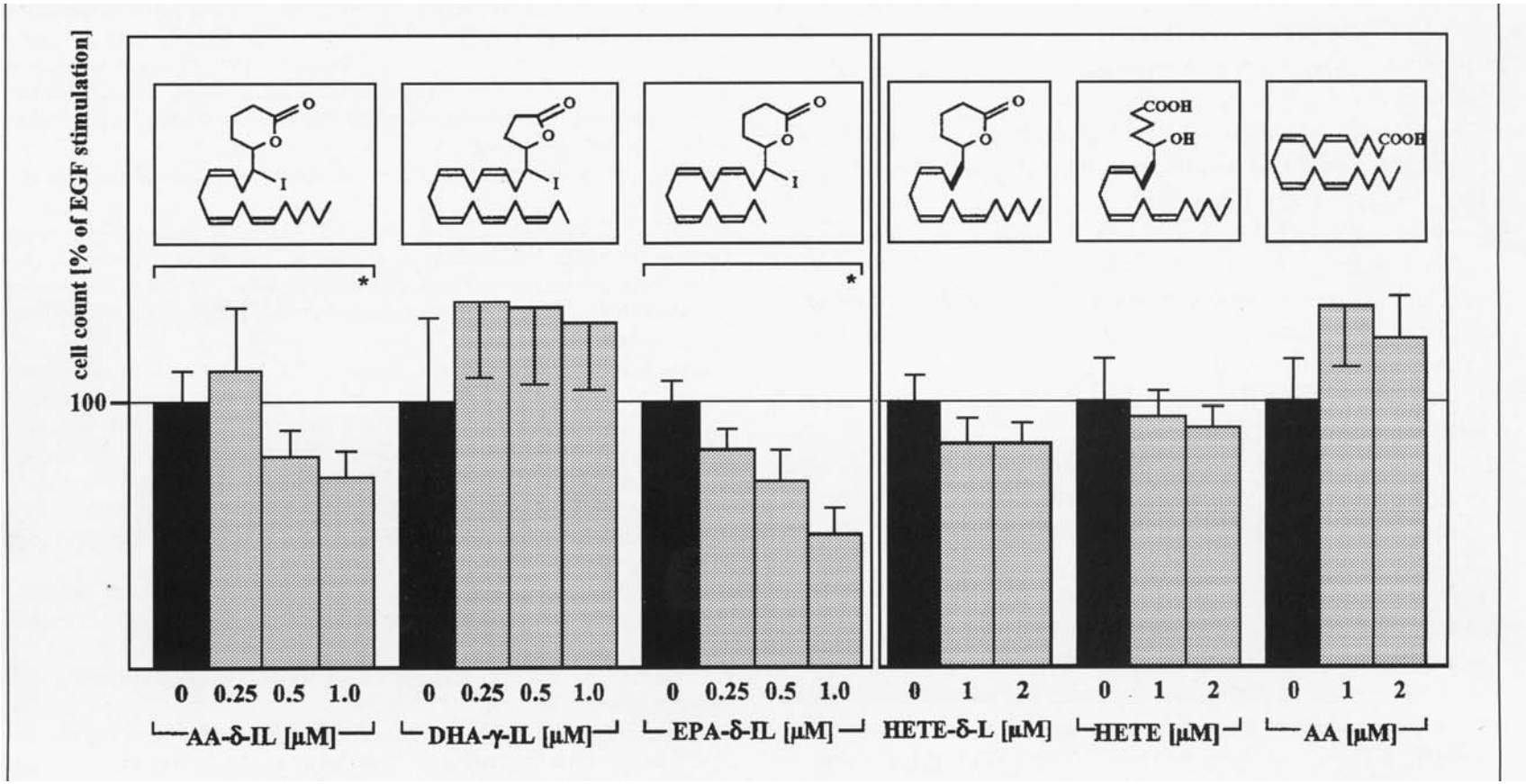


Iodolactones synthesized in vitro

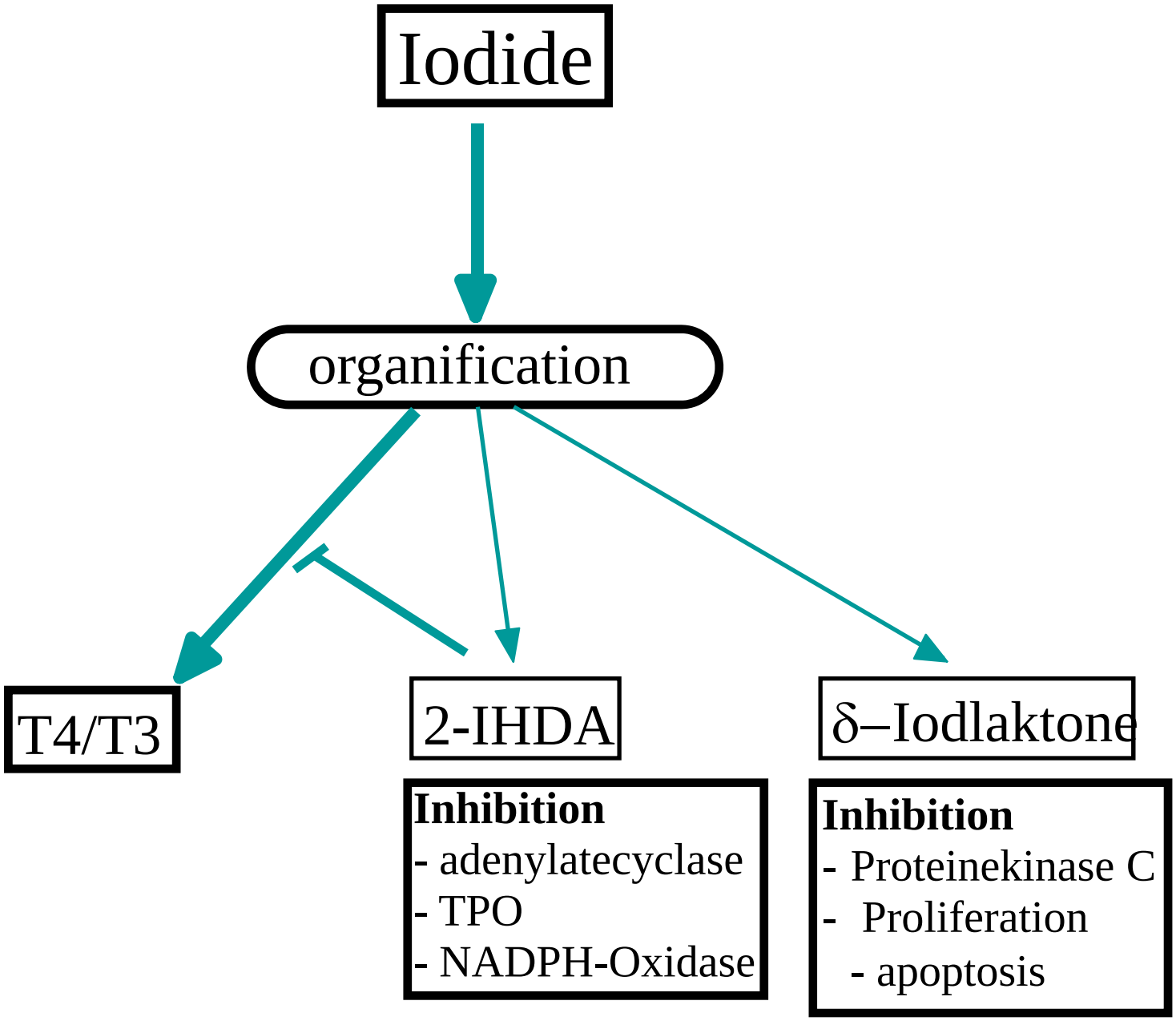


Gärtner et al 1996

Effect of different iodolactones on apoptosis in thyroid follicles



Gärtner et al 1996


Iodide
organification
T4/T3
2-IHDA
δ–Iodlaktone
Inhibition
- adenylatecyclase
- TPO
- NADPH-Oxidase
Inhibition
- Proteinekinase C
- Proliferation
- apoptosis

Breast cancer in association with thyroid disorders

Orhan Turken[1], Yavuz Narın[2], Sezai Demırbas[3], M Emin Onde[4], Ozkan Sayan[5], E Gokhan Kandemır[1], Mustafa Yaylacı[1] and Ahmet Ozturk[5]

Breast Cancer Research Vol 5 No 5 , **2005**

Table 1

Patient distribution according to clinical and ultrasound evaluation of thyroid gland

	Patients (*n* [%])	Control (*n* [%])	*P*
Normal gland	63 (42)	70 (70)	0.001
Diffuse goitre	12 (8)	4 (4)	0.29
Nodular goitre	75 (50)	26 (26)	0.001

Table 3

Classification of patients in relation to functional thyroid diseases

	Patients (*n* [%])	Control (*n* [%])	*P*
Hyperthyroidism	6 (4)	1 (1)	0.24
Hypothyroidism	4 (3)	–	0.152
Nontoxic goitre	77 (51)	29 (29)	0.001

Mammacarcinome häufiger assoziiert sowohl mit MNG als auch mit AIT

Jodmangel assoziiert mit Mammacarcinomen

Table 4

Classification of patients based on autoimmune and non-autoimmune thyroid disorders

	Patients (*n* [%])	Controls (*n* [%])	*P*
Normal	54 (36)	74(74)	0.0001
Non-AITD	39 (26)	9 (9)	0.001
Autoimmune thyroiditis	57 (38)	17 (17)	0.001

AITD, autoimmune thyroid disease.

Mammakarzinom und Schilddrüse

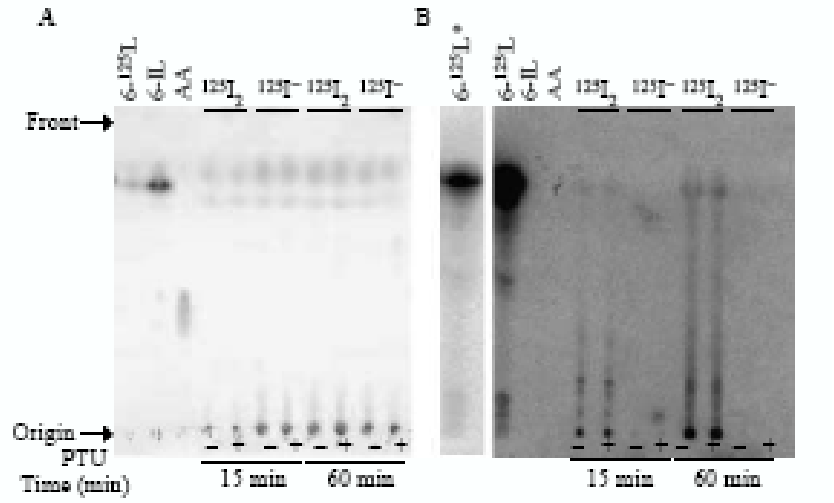
Mammakarzinom und Struma		**10 %**
Alterkorr. Kontrollen		**5 %**
T0	**Struma**	**28,5 %**
T1		**40,3 %**
T2		**38,2 %**
T3-T4		**63,6 %**

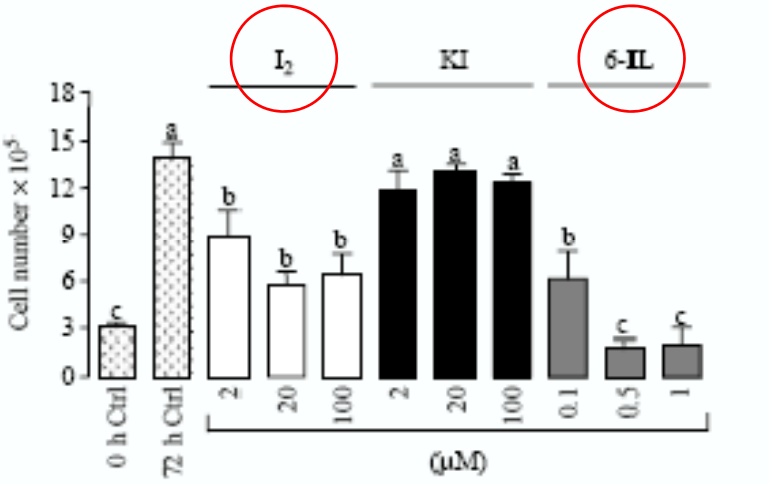
Smyth PPA et al JCEM 1996

Uptake and antiproliferative effect of molecular iodine in the MCF-7 breast cancer cell line

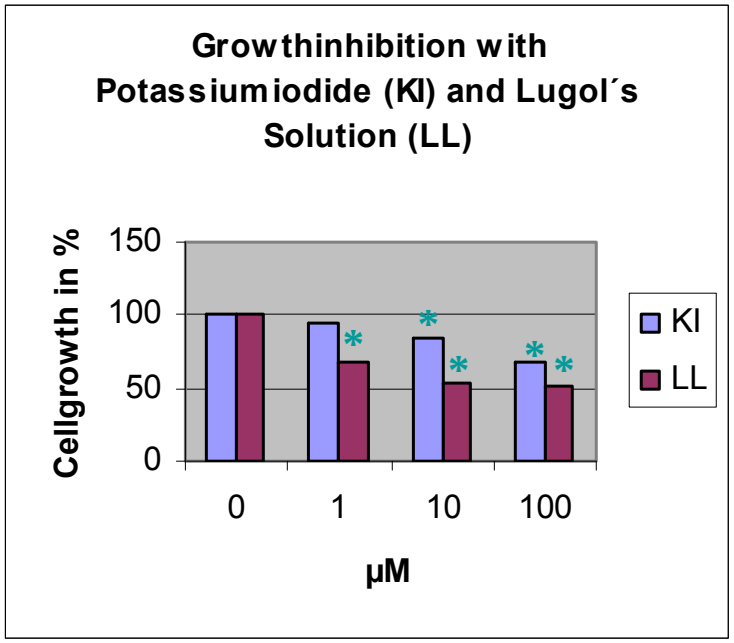
Endocrine-Related Cancer (2006) 13 1147–1158

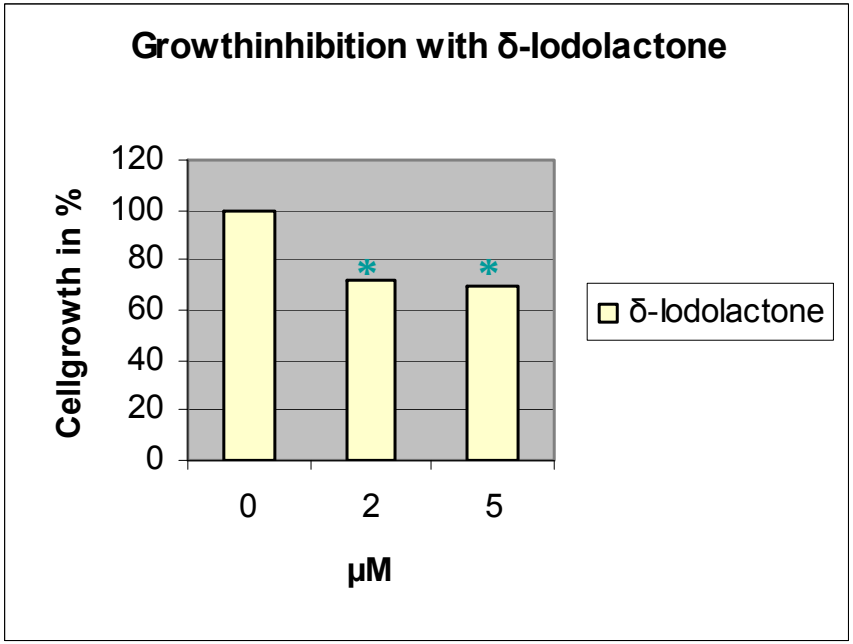
O Arroyo-Helguera, B Anguiano, G Delgado and C Aceves





Growth inhibition of MCF 7 cell with iodine and δ-iodolactone

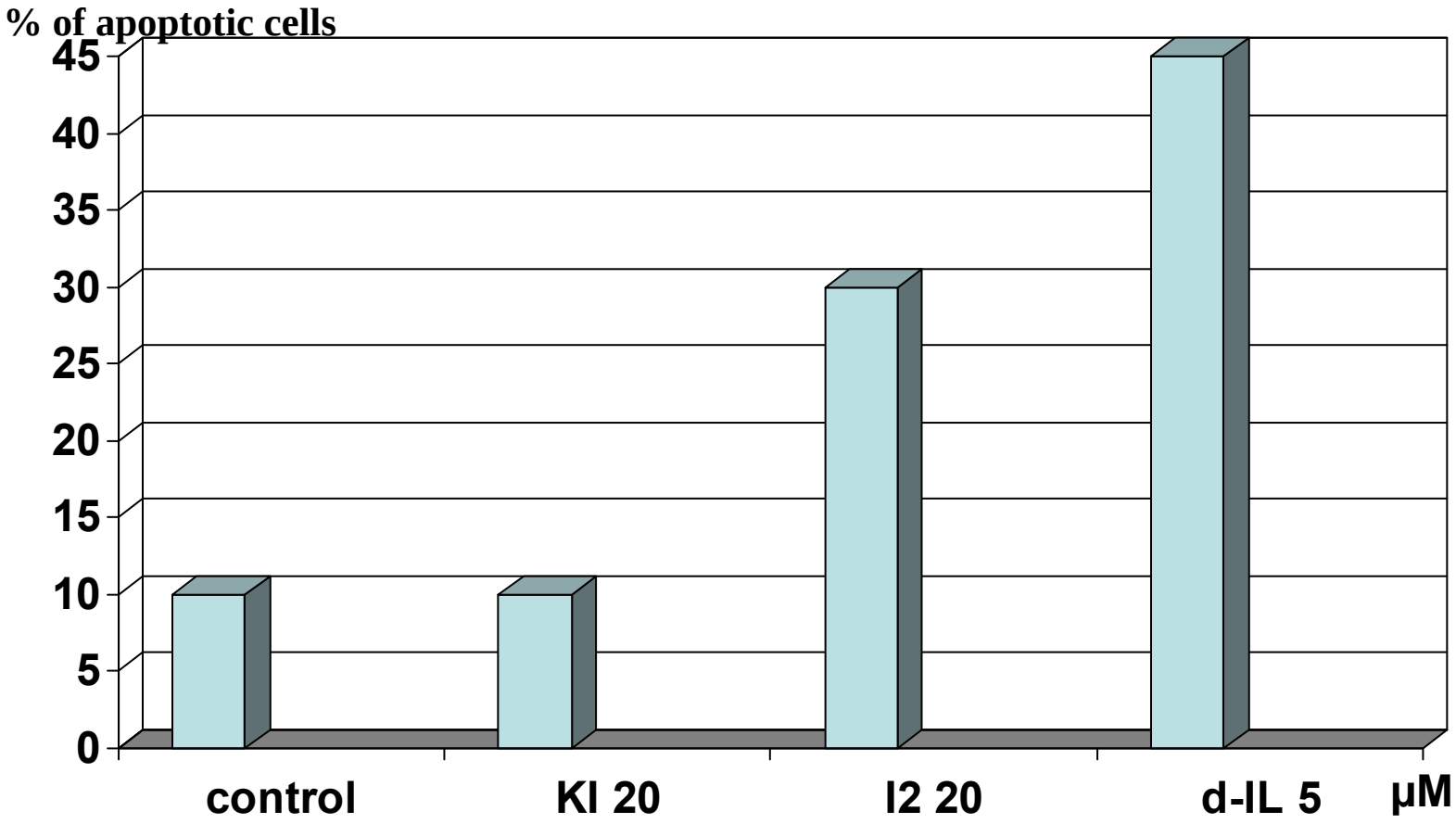




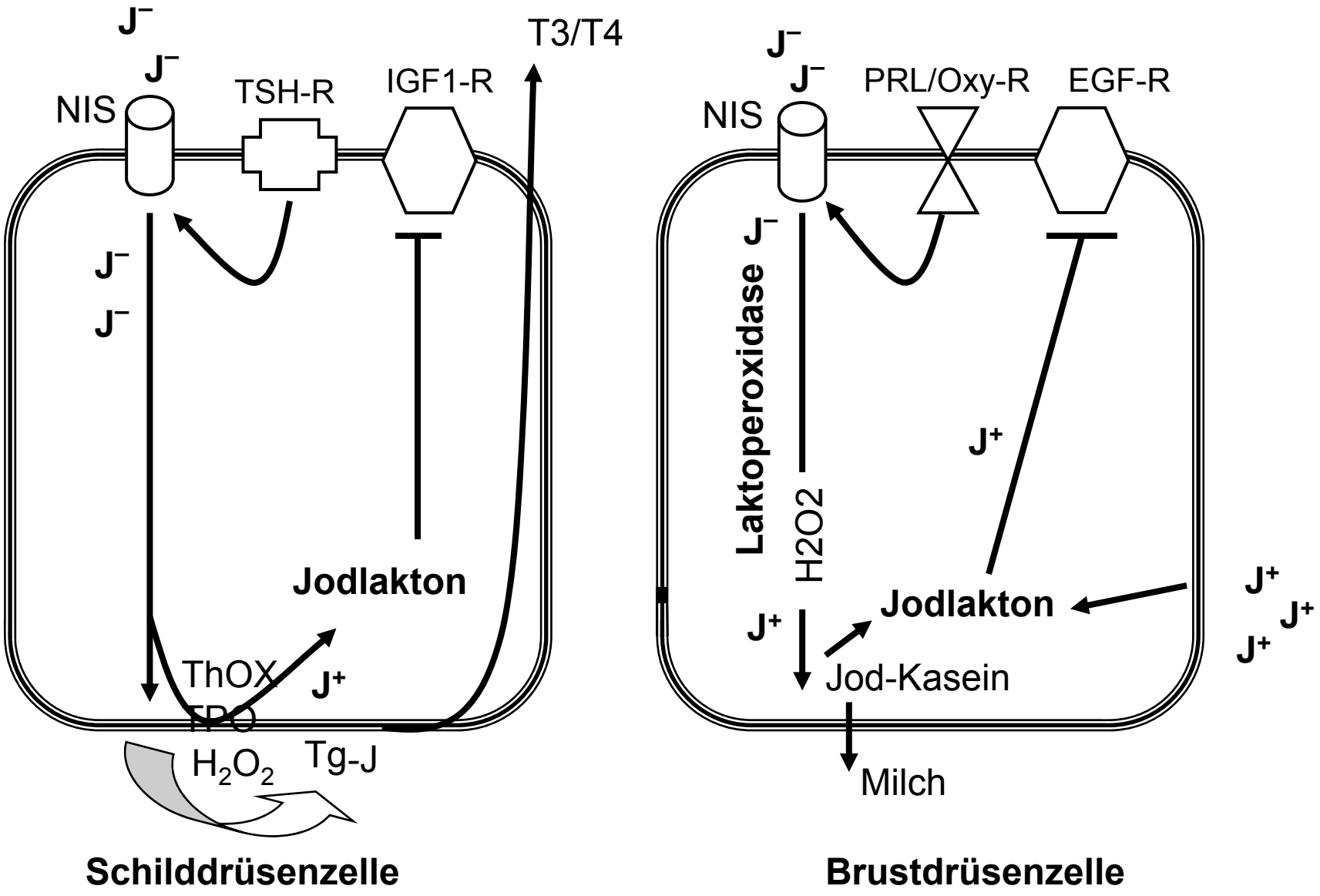
*** p< 0.05**

Gärtner et al. ETA 2007

Incidence of apoptotic cells (MCF 7)



Gärtner et al. ETA 2007


J⁻
J⁻
NIS
TSH-R
IGF1-R
T3/T4
J⁻
J⁻
Jodlakton
ThOX
J⁺
TPO
H2O2
Tg-J
Schilddrüsenzelle
J⁻
J⁻
NIS
PRL/Oxy-R
EGF-R
J⁻
Laktoperoxidase
H2O2
J⁺
J⁺
Jodlakton
J⁺
J⁺
J⁺
Jod-Kasein
Milch
Brustdrüsenzelle

Iodine Alters Gene Expression in the MCF7 Breast Cancer Cell Line: Evidence for an Anti-Estrogen Effect of Iodine

Int. J. Med. Sci. 2008, 5

Frederick R. Stoddard II [1,2], Ari D. Brooks[1], Bernard A. Eskin[3], and Gregg J. Johannes[2]

A. 29 Genes that are Up-Regulated[4] in Response to Iodine Treatment[5]

Cell Cycle/Proliferation			Fold Change
NM_001673	ASNS	asparagine synthetase	4
L24498	GADD45A	growth arrest and DNA-damage-inducible, alpha[3]	2
Steroid Metabolism			
NM_000104	CYP1B1	cytochrome P450, family 1, subfamily B, polypeptide 1[3]	11.3
NM_001353	AKR1C1	aldo-keto reductase family 1, member C1[3]	6
NM_000499	CYP1A1	cytochrome P450, family 1, subfamily A, polypeptide 1[3]	2.5
Transcription			
NM_003900	SQSTM1	sequestosome 1	2.8
AB095432	TSC22D3	delta sleep inducing peptide, immunoreactor	2.6
DNA repair			
NM_019058	DDIT4	DNA-damage-inducible transcript 4	2.2
L24498	GADD45A	growth arrest and DNA-damage-inducible, alpha[3]	2.0
Lipid Metabolism			
NM_000693	ALDH1A3	aldehyde dehydrogenase 1 family, member A3	3.2
NM_004315	ASAH1	N-acylsphingosine amidohydrolase (acid ceramidase) 1	2.2
tRNA synthesis			
NM_004184	WARS	tryptophanyl-tRNA synthetase	3
NM_002047	GARS	glycyl-tRNA synthetase	2.3
NM_003680	YARS	tyrosyl-tRNA synthetase	2
Other			
NM_021158	TRIB3	tribbles homolog 3 (Drosophila)	4
NM_005218	DEFB1	defensin, beta 1	3.3
NM_033197	C20orf114	chromosome 20 open reading frame 114	2.7
NM_004753	DHRS3	dehydrogenase/reductase (SDR family) member 3	2.7
NM_002083	GPX2	glutathione peroxidase 2 (gastrointestinal)[3]	2.5
NM_006636	MTHFD2	methylene tetrahydrofolate dehydrogenase	2.5
AF104032	SLC7A5	solute carrier family 7, member 5	2.4
NM_004864	GDF15	growth differentiation factor 15	2.2
NM_000416	IFNGR1	interferon gamma receptor 1	2.1
NM_002356	MARCKS	myristoylated alanine-rich protein kinase C substrate	2.0
Function Unknown			
AK001064	LOC86026	hypothetical protein DKFZp434P055	3.5
AK054816	ORAOV1	oral cancer overexpressed 1	3.0
NM_006470	TRIM16	tripartite motif-containing 16	2.4
AF245505	MXRA5	matrix remodelling associated 5	2.3
AL162069	LOC144501	hypothetical protein LOC144501	2.2
BE884686	LTB4DH	leukotriene B4 12-hydroxydehydrogenase	2.1

Iodine Alters Gene Expression in the MCF7 Breast Cancer Cell Line: Evidence for an Anti-Estrogen Effect of Iodine

Int. J. Med. Sci. 2008, 5

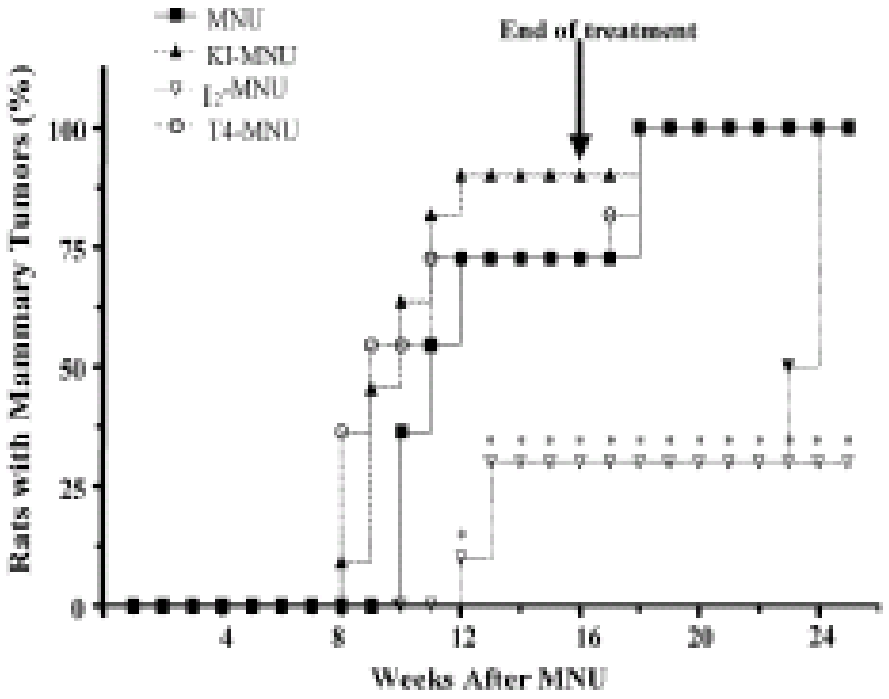
Frederick R. Stoddard II [1,2], Ari D. Brooks[1], Bernard A. Eskin[3], and Gregg J. Johannes[2]

B. 14 Genes that are Down-Regulated[4] in Response to Iodine Treatment[2]			
Estrogen responsive genes			Fold Change
NM_003225	TFF1	trefoil factor 1 (estrogen-inducible sequence) [3]	-2.3
NM_003881	WISP2	WNT1 inducible signaling pathway protein 2[3]	-2.4
Cell Cycle genes			
NM_003258	TK1	thymidine kinase 1, soluble	-3.7
NM_002305	LGALS1	lectin, galactoside-binding, soluble, 1 (galectin 1)	-2.6
NM_007019	UBE2C	ubiquitin-conjugating enzyme E2C	-2.5
NM_001071	TYMS	thymidylate synthetase	-2.3
NM_053056	CCND1	cyclin D1 (PRAD1: parathyroid adenomatosis 1) [3]	-2.0
NM_002466	MYBL2	v-myb myeloblastosis viral oncogene homolog like 2[3]	-2.2
Cell Growth/Proliferation Genes			
NM_005264	GFRA1	GDNF family receptor alpha 1[3]	-2.5
NM_007161	LGT1	leukocyte specific transcript 1	-2.5
Ion Transport Genes			
NM_004669	CLIC3	chloride intracellular channel 3	-2.2
Chromatin Organization			
NM_002105	H2AFX	H2A histone family, member X	-2.2
Function Unknown			
NM_007173	PRSS23	protease, serine, 23	-3.7
NM_006408	AGR2	anterior gradient 2 homolog (Xenopus laevis)	-2.1

Inhibition of *N*-methyl-*N*-nitrosourea-induced mammary carcinogenesis by molecular iodine (I_2) but not by iodide (I^-) treatment Evidence that I_2 prevents cancer promotion

Pablo García-Solís [a], Yunuen Alfaro [a], Brenda Anguiano [a], Guadalupe Delgado [a], Raphael C. Guzman [b], Satyabrata Nandi [b], Mauricio Díaz-Muñoz [a], Olivia Vázquez-Martínez [a], Carmen Aceves [a,*]

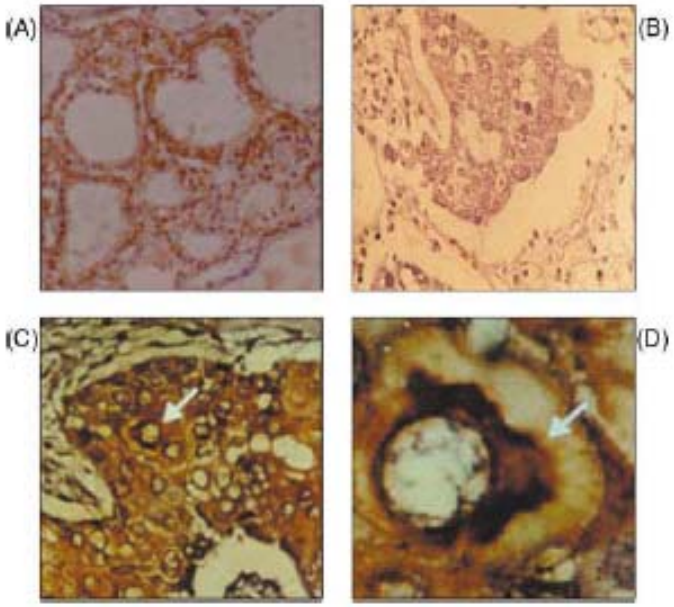
Molecular and Cellular Endocrinology 236 (2005) 49–57

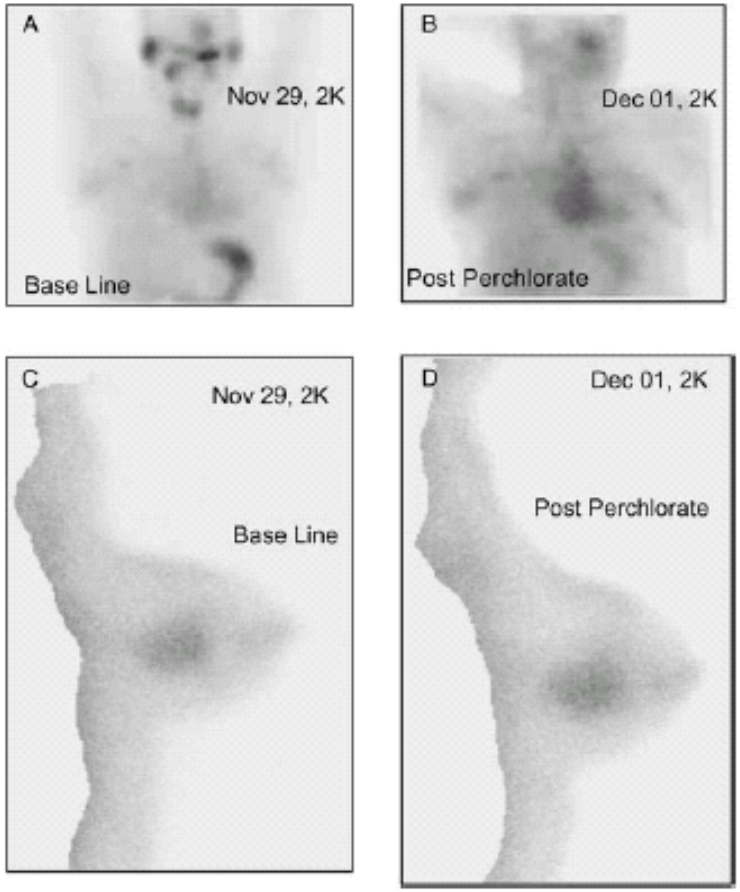


Functional expression of sodium iodide symporter (NIS) in human breast cancer tissue*

Geeta Upadhyay[1], Rajesh Singh[1], Gaurav Agarwal[2], Saroj K. Mishra[2], Lily Pal[3], Prasanta K. Pradhan[4], Birendra K. Das[4], and Madan M. Godbole[1]

Breast Cancer Research and Treatment 77: 157–165, 2003.





APOPTOTIC AND ANTIPROLIFERATIVE EFFECTS OF IODINE SUPPLEMENTS ON HUMAN BREAST CANCER TUMORS

L. VEGA-RIVEROLL[1], J. ROJAS-AGUIRRE[2], J. ROMERO-ROMO[3], G. DELGADO[1], P. MONDRAGON[1], C. ACEVES[1]

- Frauen mit bioptisch gesichertem Mamma-Karzinom
- 2-5 Wochen vor Operation Behandlung mit 5 mg Lugol´scher Lösung /Tag oder Placebo
- Proliferationsrate 0,46 ± 0,19 vs 1,61 ± 0,39
- Bax/Bcl2 Quotient und Apoptoserate signifikant erhöht unter Jod
- p53 unverändert
- TSH und FT4 unverändert

Schlußfolgerung

- Bisherige Datenlage lässt den Schluss zu, dass es einen möglichen Zusammenhang zwischen Jodmangel und Brustkrebs gibt
- Forschung auf diesem Gebiet muss intensiviert werden
- Eine ausreichend hohe Jodprophylaxe mit 500-1000 µg Jod pro Tag könnte dazu beitragen die Inzidenz von Brustkrebs zu vermeiden.
- Eine adjuvante Jodtherapie bei Mammakarzinom scheint möglicherweise sinnvoll zu sein und muss in kontrollierten Studien untersucht werden (Sekundär-Prophylaxe)