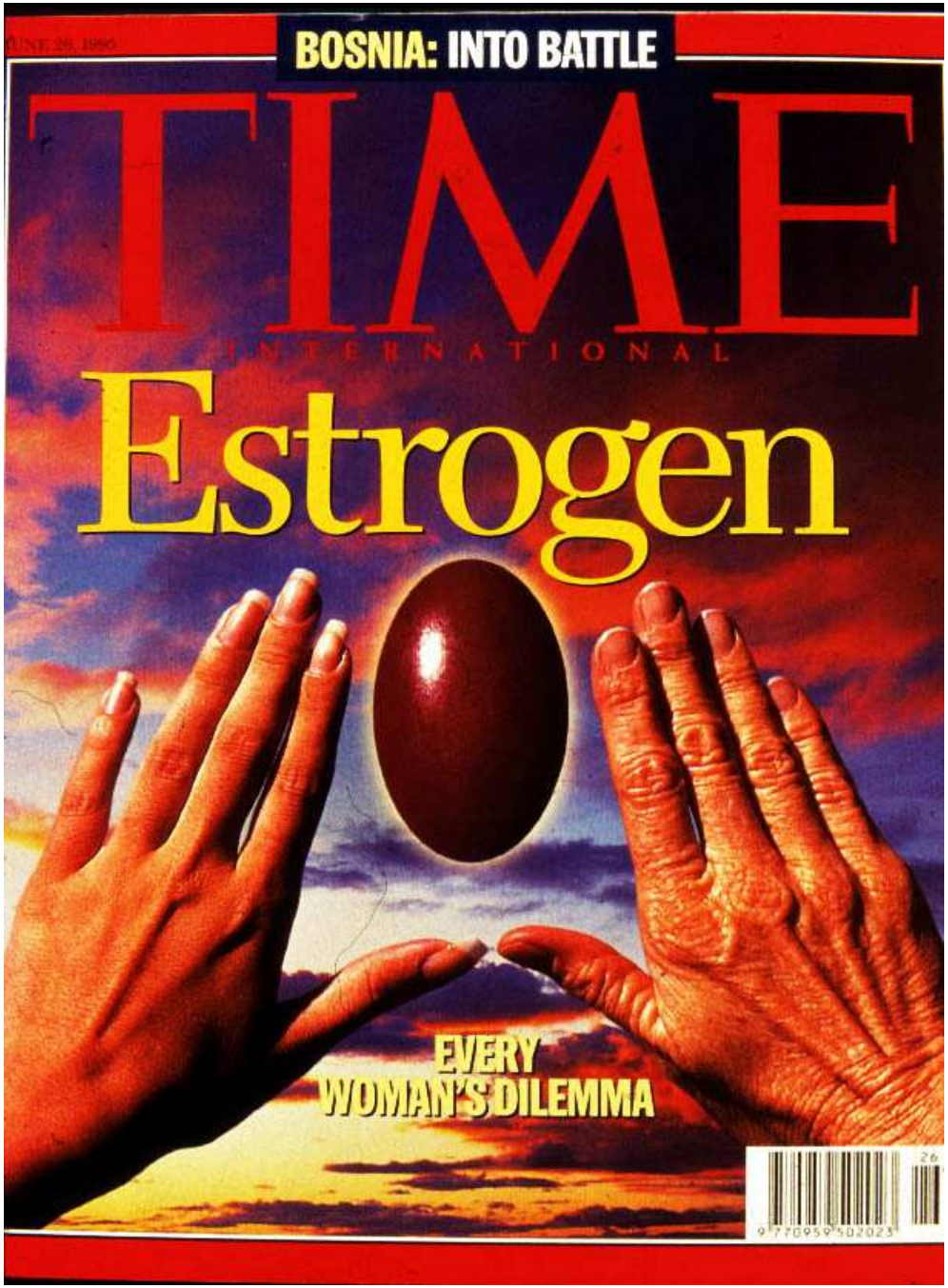
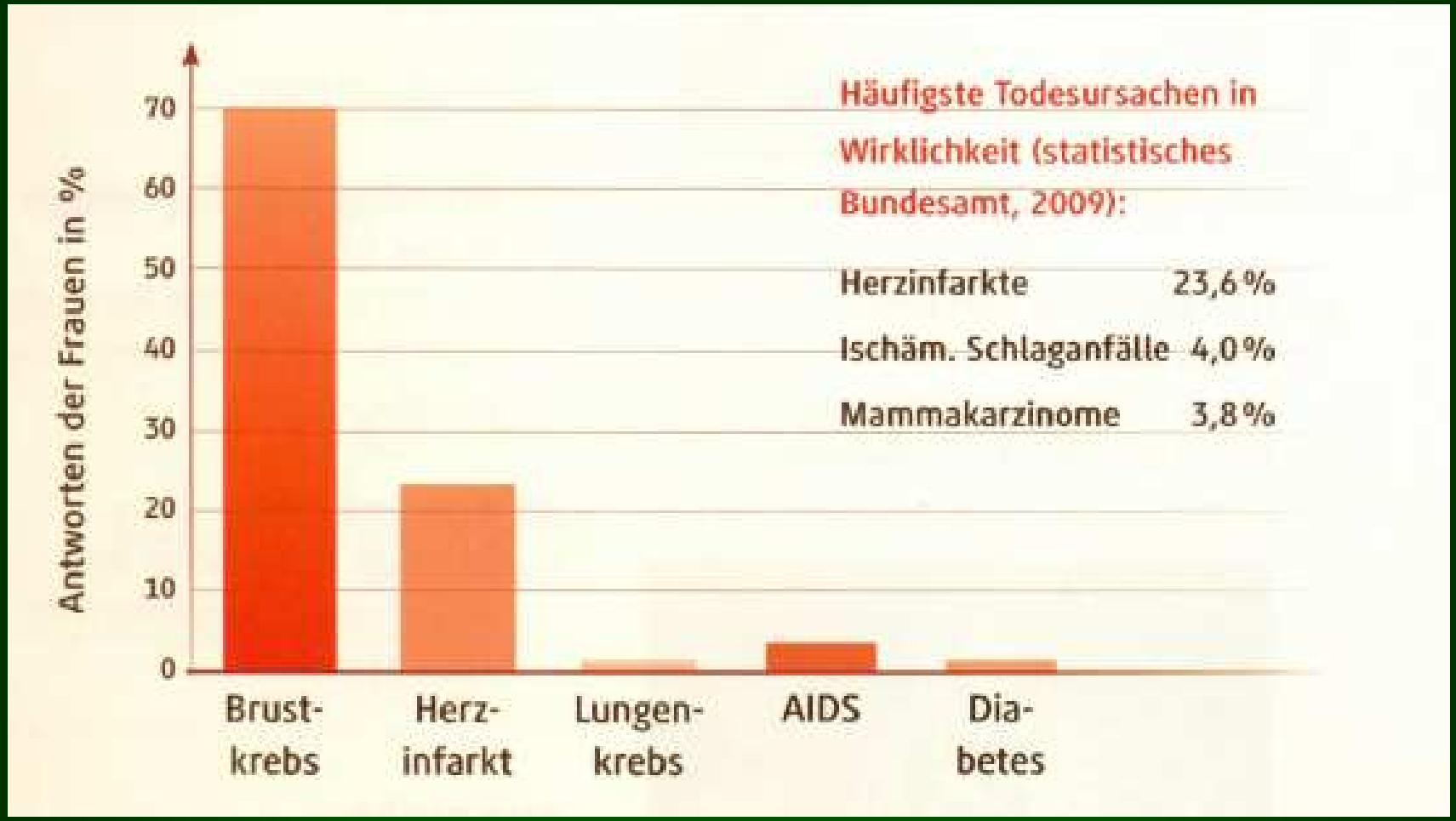

JUNE 26, 1995
BOSNIA: INTO BATTLE
TIME
INTERNATIONAL
Estrogen
EVERY
WOMAN'S DILEMMA


Antworten der Frauen in %
70
60
50
40
30
20
10
0
Brust-krebs
Herz-infarkt
Lungen-krebs
AIDS
Dia-betes
Häufigste Todesursachen in Wirklichkeit (statistisches Bundesamt, 2009):
Herzinfarkte 23,6 %
Ischäm. Schlaganfälle 4,0 %
Mammakarzinome 3,8 %

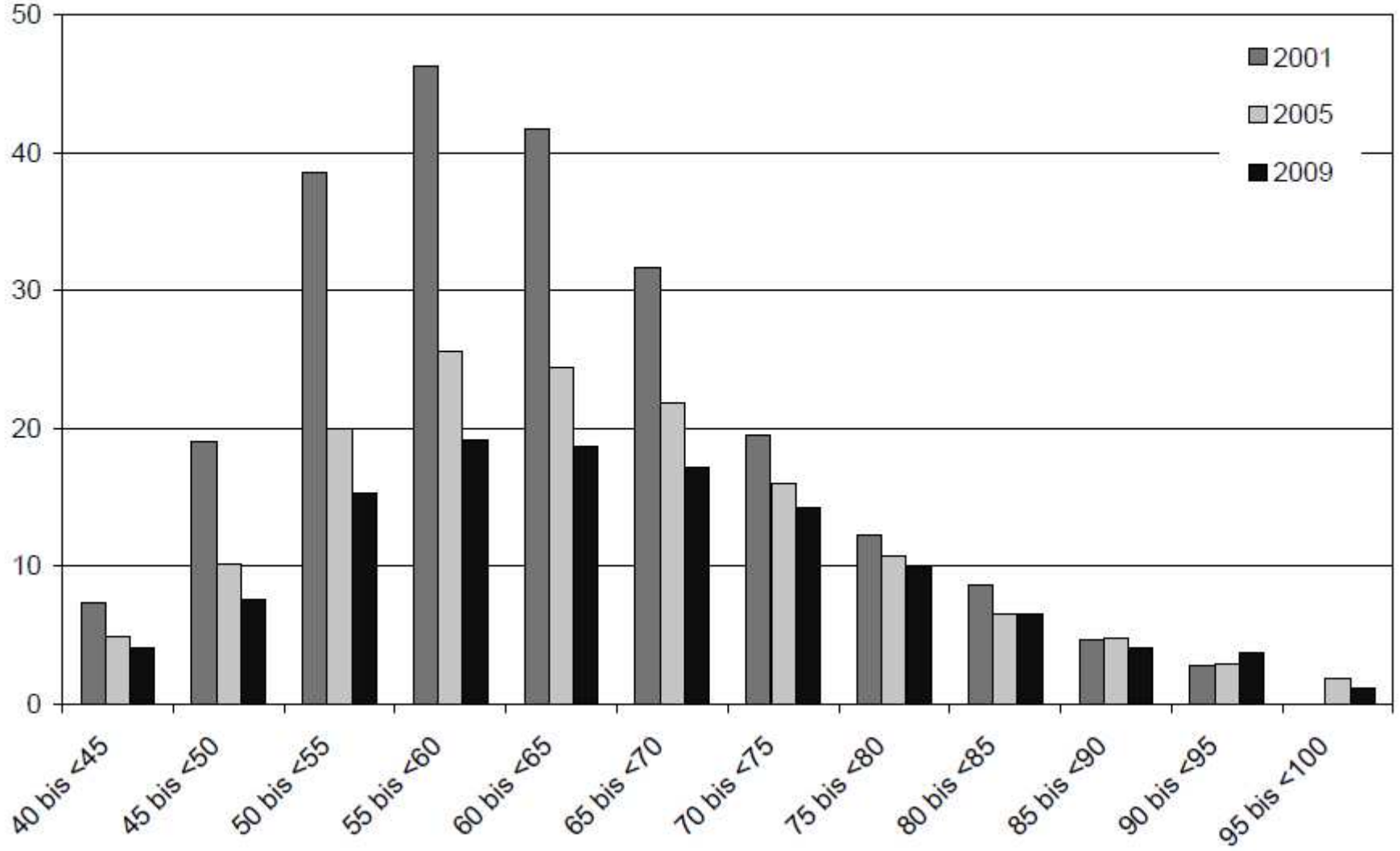
Spezielle Analysen zu den einzelnen Indikationsgebieten

Brustkrebserkrankungen bei Frauen und der Einfluss der Hormontherapie in und nach den Wechseljahren

Cornelia Gerdau-Heitmann

BARMER GEK Arzneimittel-Report 2010
Schriftenreihe zur Gesundheitsanalyse, Band 2: 1-224
Gerdau-Heitmann C. Kapitel 3, 99-109

Abbildung 3.1.2 Altersspezifische HT-Verordnungsprävalenz der Jahre 2001, 2005 und 2009 in Prozent

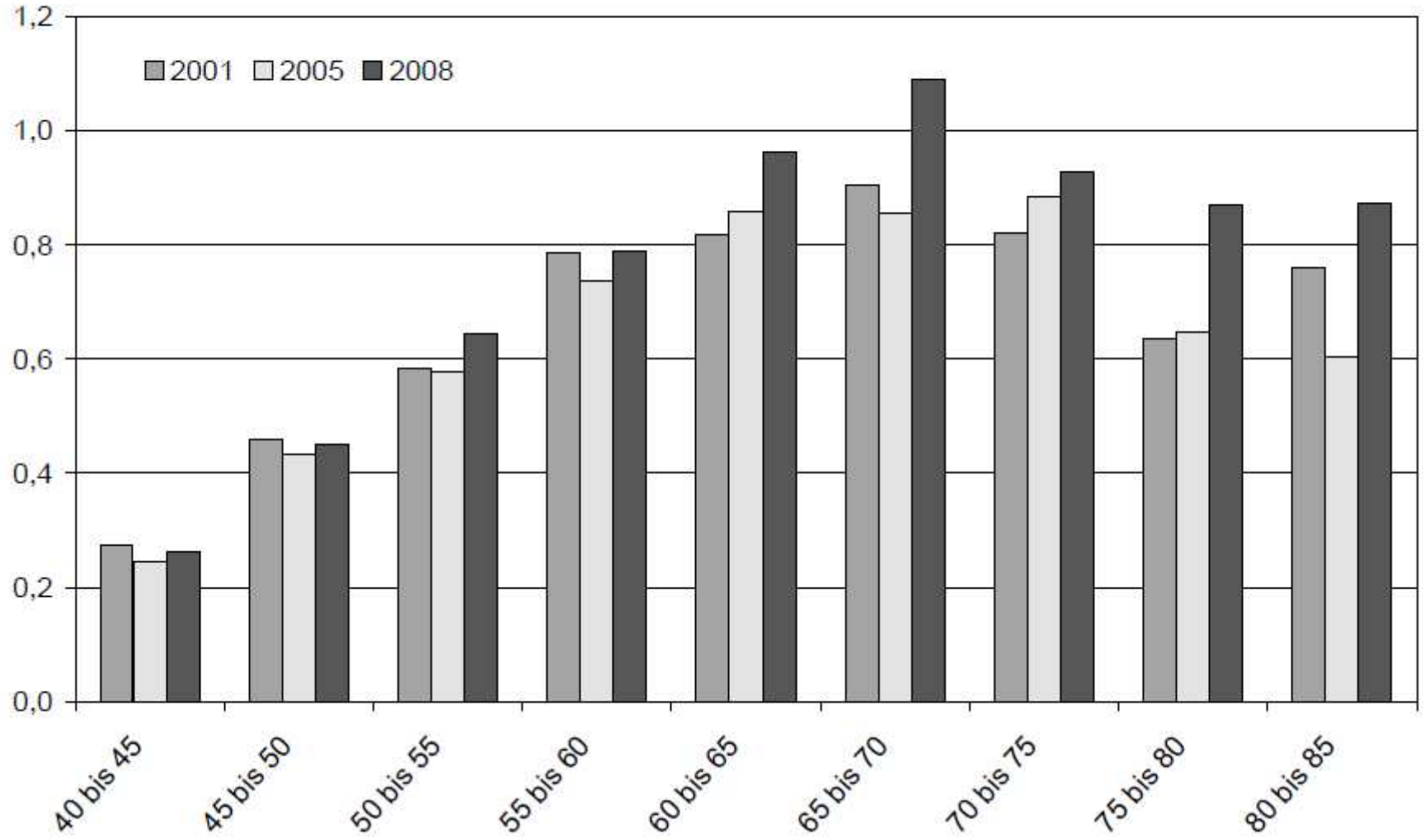


BARMER GEK Arzneimittel-Report 2010, Schriftenreihe zur Gesundheitsanalyse, Band 2: 1-224
Gerdau-Heitmann C. Kapitel 3, 99-109

In Bezug auf das Jahr 2001 lässt sich dagegen nahezu eine Halbierung der HT-Verordnungsprävalenz feststellen. Die Abbildung 3.1.2 zeigt die altersspezifischen HT-Verordnungsprävalenzen. Vergleicht man die Ergebnisse mit denen im Jahr 2001, so zeigt sich, dass im Altersbereich zwischen 50 und unter 70 Jahren nicht mehr jede zweite bis dritte Frau eine Verordnung aufweist, sondern nur noch jede fünfte bis sechste Frau.

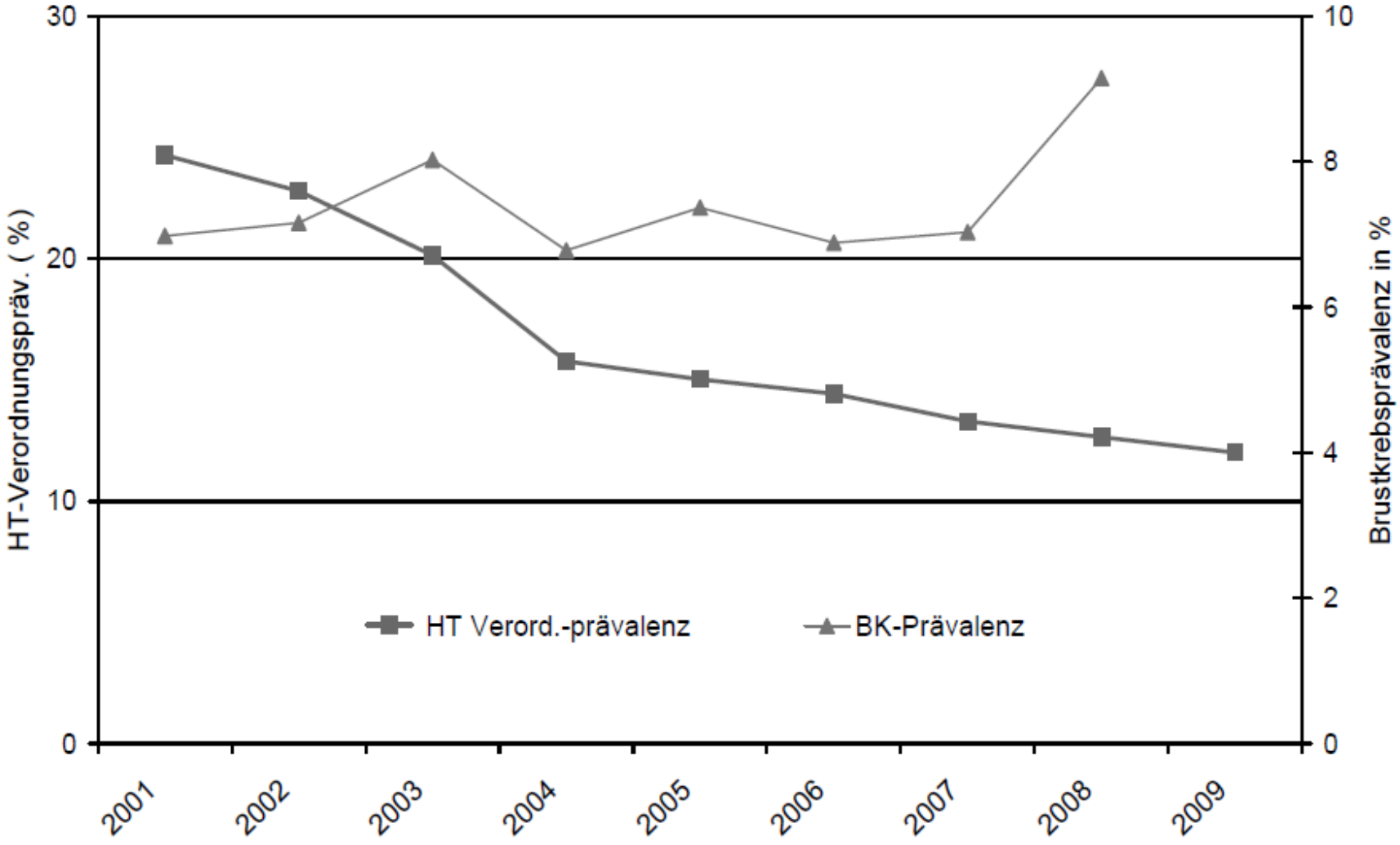
BARMER GEK Arzneimittel-Report 2010
Schriftenreihe zur Gesundheitsanalyse, Band 2: 1-224
Gerdau-Heitmann C. Kapitel 3, 99-109

Abbildung 3.1.3 Altersspezifische Brustkrebsprävalenz der Jahre 2001, 2005 und 2008 in Prozent



BARMER GEK Arzneimittel-Report 2010, Schriftenreihe zur Gesundheitsanalyse, Band 2: 1-224
Gerdau-Heitmann C. Kapitel 3, 99-109

Abbildung 3.1.1 Altersstandardisierte HT-Verordnungsprävalenz der Jahre 2001 bis 2009 sowie die Brustkrebsprävalenz von 2001 bis 2008



BARMER GEK Arzneimittel-Report 2010, Schriftenreihe zur Gesundheitsanalyse, Band 2: 1-224
Gerdau-Heitmann C. Kapitel 3, 99-109

Anhand der Arzneiverordnungsdaten wurde anschließend ermittelt, welche Frauen Hormone im Untersuchungszeitraum von 2001bis 2008 verschrieben bekamen und welche Frauen in den stationären Daten die Diagnose Brustkrebs aufwiesen. Die Auswertung mit der Prozedur Proc logistic zeigte jedoch einen erniedrigten Wert mit einem OR = 0,666 (95 % KI = 0,571 – 0,778)..

BARMER GEK Arzneimittel-Report 2010
Schriftenreihe zur Gesundheitsanalyse, Band 2: 1-224
Gerdau-Heitmann C. Kapitel 3, 99-109

Die Ursache für dieses Ergebnis dürfte am ehesten im Studiendesign sowie der nicht ausreichenden Datenbasis zu suchen sein. Keinesfalls darf dieses Ergebnis so interpretiert werden, dass Hormone vor Brustkrebs schützen

BARMER GEK Arzneimittel-Report 2010
Schriftenreihe zur Gesundheitsanalyse, Band 2: 1-224
Gerdau-Heitmann C. Kapitel 3, 99-109

KOMMENTAR

HORMONERSATZTHERAPIE

Ein Drittel weniger Brustkrebs-Diagnosen unter HRT

Barmer GEK Arzneimittel-Report 2010 mit kaum bekanntem Ergebnis

J. Matthias Wenderlein

Im Arzneimittel-Report 2010 der Barmer GEK stieß der Autor auf einige bemerkenswerte Ergebnisse zum Thema HRT, die er im Folgenden mit kurzen Anmerkungen versehen vorstellt.

Wenderlein JM. FRAUENARZT 2011;52(6):558-559

ONCOLOGY

Reduced incidence of distant metastases and lower mortality in 1072 patients with breast cancer with a history of hormone replacement therapy

Florian Schuetz, MD; Ingo J. Diel, MD; Marit Pueschel, MD; Thomas von Holst, MD; Erich F. Solomayer, MD; Stefan Lange, MD; Peter Sinn, MD; Gunther Bastert, MD; Christof Sohn, MD

PRIMÄRE METASTASEN

PRIOR HRT USER **1,9%**

p>0,001

PRIOR NON HRT USER **7%**

Florian Schuetz. Reduced incidence of distant metastases and lower mortality in 1072 patients with breast cancer with a history of hormone replacement therapy. Am J Obstet Gynecol 2007;196:342.e1-342.e9

SEKUNDÄRE METASTASEN

FREE (5 JAHRE)

NON USER	**80,6%**
HRT USER	**90,7%**

Florian Schuetz. Reduced incidence of distant metastases and lower mortality in 1072 patients with breast cancer with a history of hormone replacement therapy. Am J Obstet Gynecol 2007;196:342.e1-342.e9

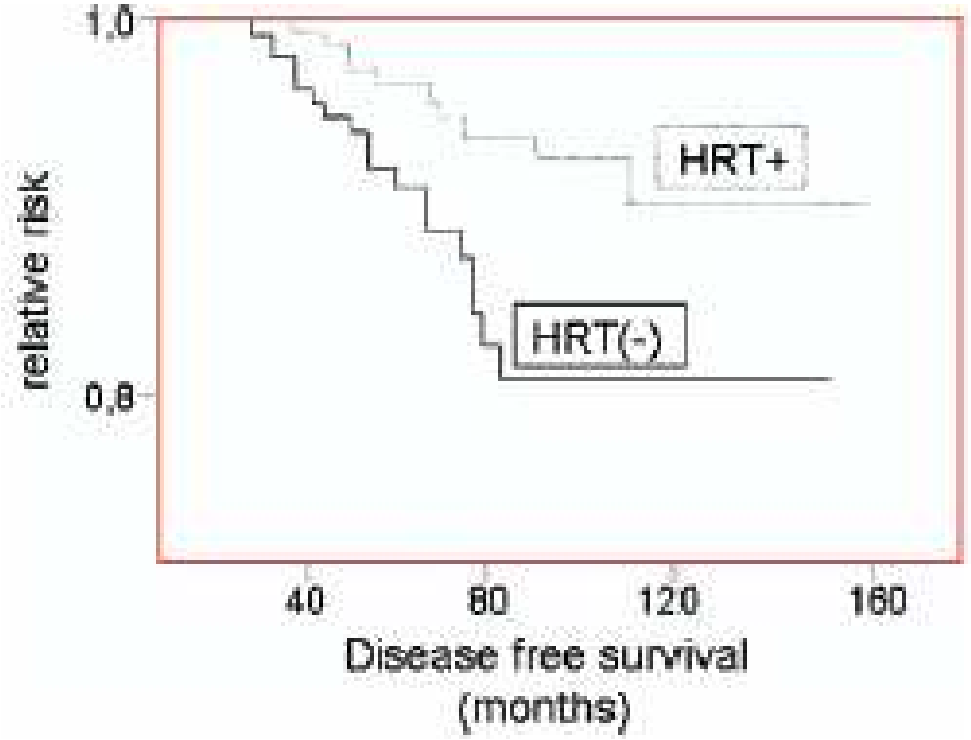
MORTALITÄT

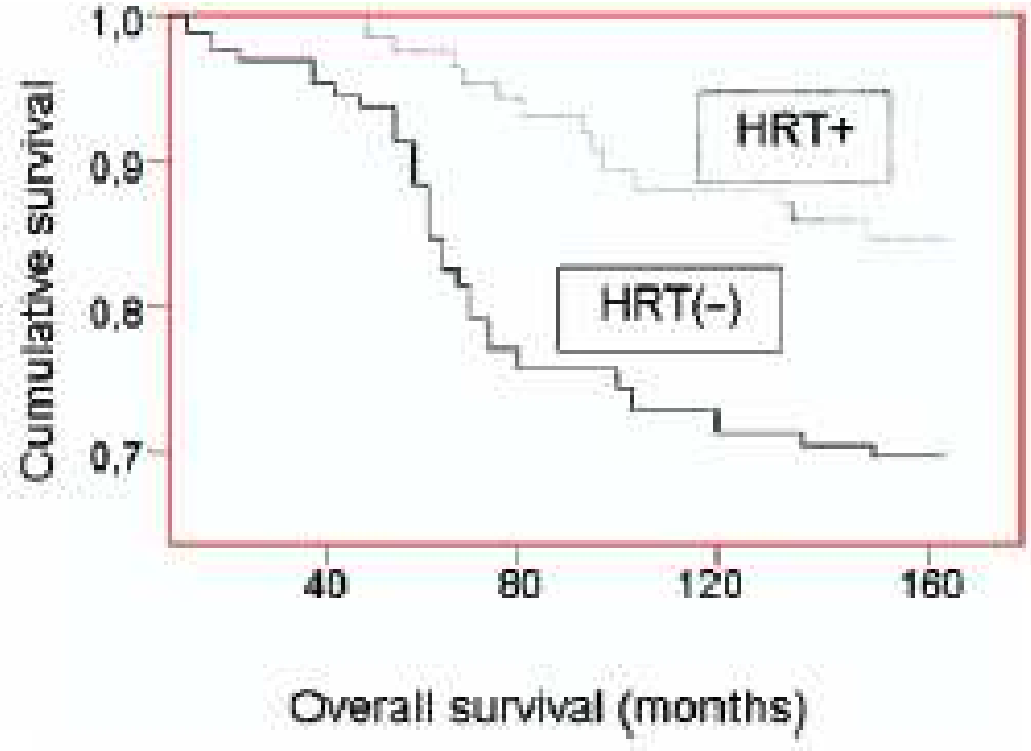
(BRUSTSPEZIFISCH)

45 MONTH

HRT USER	**7,3%**
NON USER	**21,1%**

Florian Schuetz. Reduced incidence of distant metastases and lower mortality in 1072 patients with breast cancer with a history of hormone replacement therapy. Am J Obstet Gynecol 2007;196:342.e1-342.e9


1,0
0,8
relative risk
HRT+
HRT(-)
40
80
120
160
Disease free survival
(months)


1,0
0,9
0,8
0,7
Cumulative survival
HRT+
HRT(-)
40
80
120
160
Overall survival (months)

Variable	Premenopausal group (n = 279)	Postmenopausal group		All patients (n = 1072)	*P* value*
		HRT nonuser (n = 473)	HRT user (n = 320)		
Local recurrence (n)					
All	40 (14.3%)	49 (10.4%)	25 (7.8%)	114 (10.6%)	NS
≤6 mo	2 (0.6%)	2 (0.4%)	3 (0.9%)	7 (0.7%)	
>6 mo	37 (13.3%)	45 (9.5%)	18 (5.6%)	100 (9.3%)	
Metastases (n)					
All	71 (25.4%)	120 (25.4%)	38 (11.9%)	229 (21.4%)	<.001
≤6 mo	11 (3.9%)	33 (7.0%)	6 (1.9%)	50 (4.7%)	
>6 mo	60 (21.5%)	87 (18.4%)	32 (10.0%)	179 (16.7%)	
Bone metastases (n)					
All	47 (16.8%)	68 (14.4%)	20 (6.2%)	135 (12.6%)	<.001
≤6 mo	5 (1.8%)	16 (3.4%)	2 (0.6%)	23 (2.1%)	
>6 mo	41 (14.7%)	50 (10.6%)	18 (5.6%)	109 (10.2%)	

Variable	Premenopausal group (n = 279)	Postmenopausal group		All patients (n = 1072)	*P* value*
		HRT nonuser (n = 473)	HRT user (n = 320)		
Liver metastases (n)					
All	21 (7.5%)	47 (9.9%)	13 (4.1%)	81 (7.6%)	<.001
≤6 mo	3 (1.1%)	14 (3.0%)	1 (0.3%)	18 (1.7%)	
>6 mo	17 (6.1%)	28 (5.9%)	11 (3.4%)	56 (5.2%)	
Lung/pulmonary metastases (n)					
All	27 (9.7%)	47 (9.9%)	13 (4.1%)	87 (8.1%)	<.001
≤6 mo	2 (0.7%)	6 (1.3%)	2 (0.6%)	10 (0.9%)	
>6 mo	24 (8.6%)	37 (7.8%)	10 (3.1%)	71 (6.6%)	
Other metastases (n)					
All	27 (10.0%)	45 (9.5%)	19 (5.9%)	92 (8.6%)	<.001
≤6 mo	4 (1.4%)	6 (1.4%)	4 (1.3%)	14 (1.3%)	
>6 mo	22 (7.9%)	32 (6.8%)	14 (4.4%)	68 (6.3%)	
Death	39 (14.0%)	100 (21.1%)	24 (7.5%)	163 (15.2%)	<.001

Rethinking Screening for Breast Cancer and Prostate Cancer

Laura Esserman, MD, MBA

Yiwey Shieh, AB

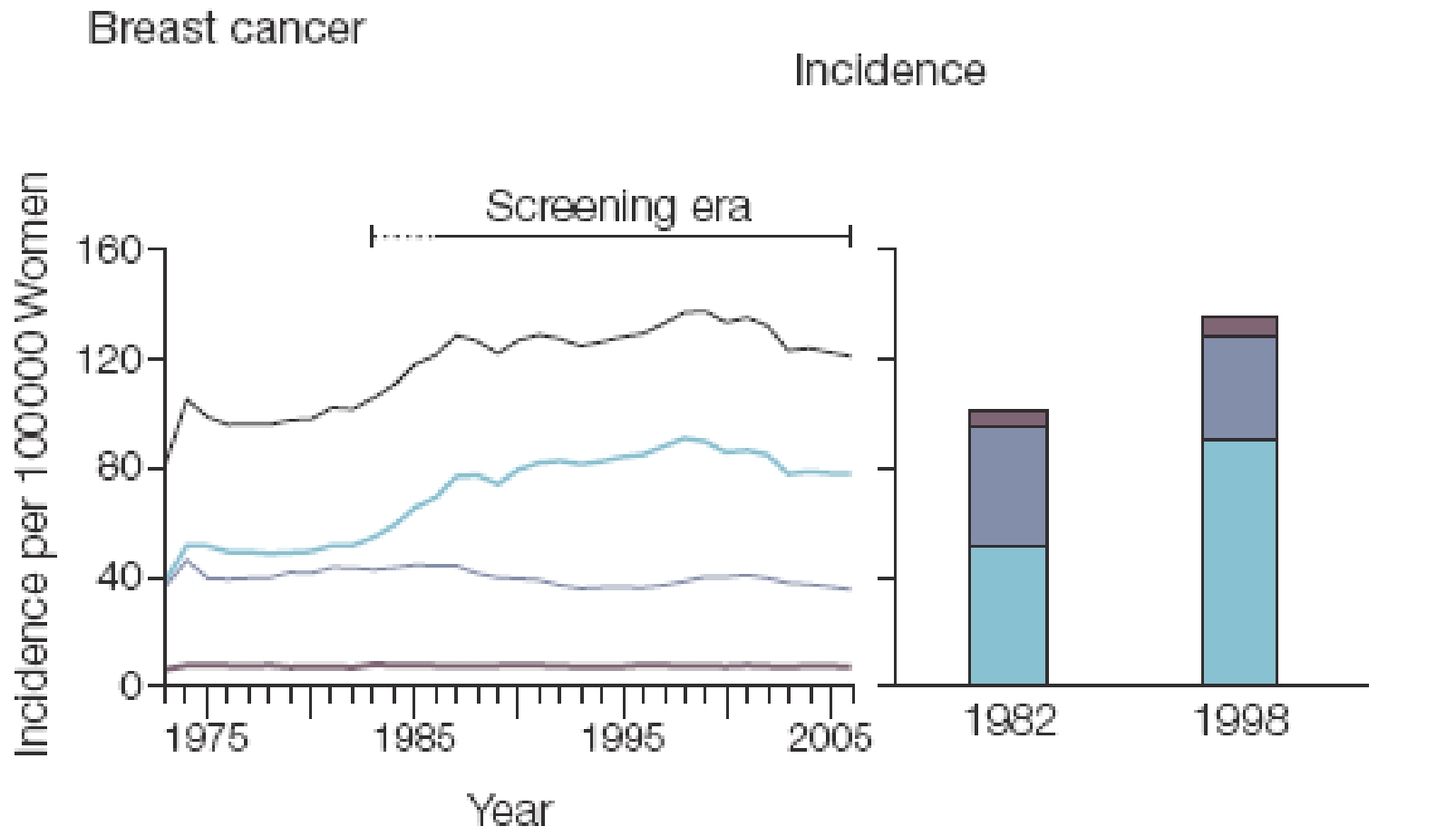
Ian Thompson, MD

After 20 years of screening for breast and prostate cancer, several observations can be made. First, the incidence of these cancers increased after the introduction of screening but has never returned to prescreening levels. Second, the increase in the relative fraction of early stage cancers has increased. Third, the incidence of regional cancers has not decreased at a commensurate rate. One possible explanation is that screening may be increasing the burden of low-risk cancers without significantly reducing the burden of more aggressively growing cancers and therefore not resulting in the anticipated reduction in cancer mortality. To reduce morbidity and mortality from prostate cancer and breast cancer, new approaches for screening, early detection, and prevention for both diseases should be considered.

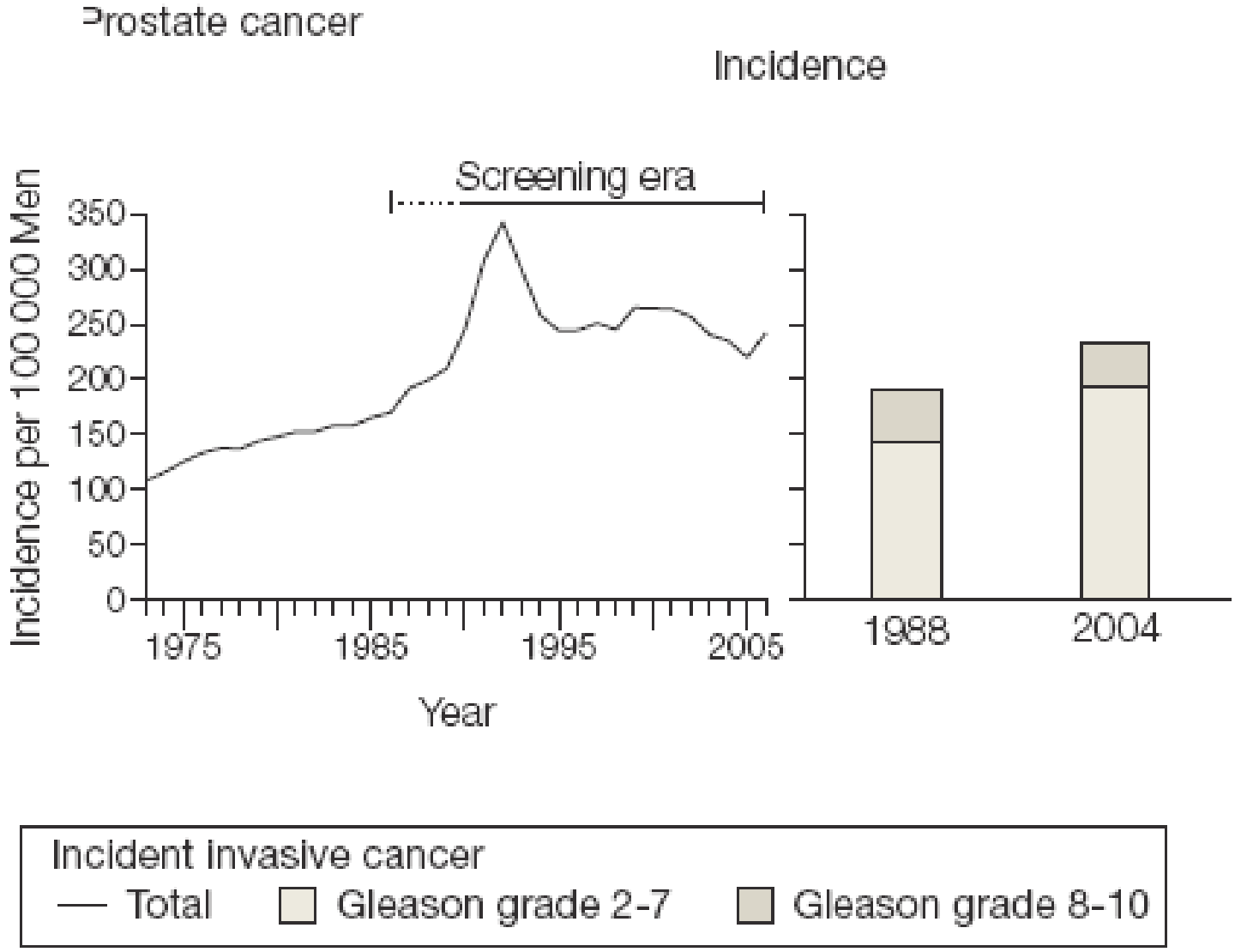
JAMA. 2009;302(15):1685-1692

www.jama.com

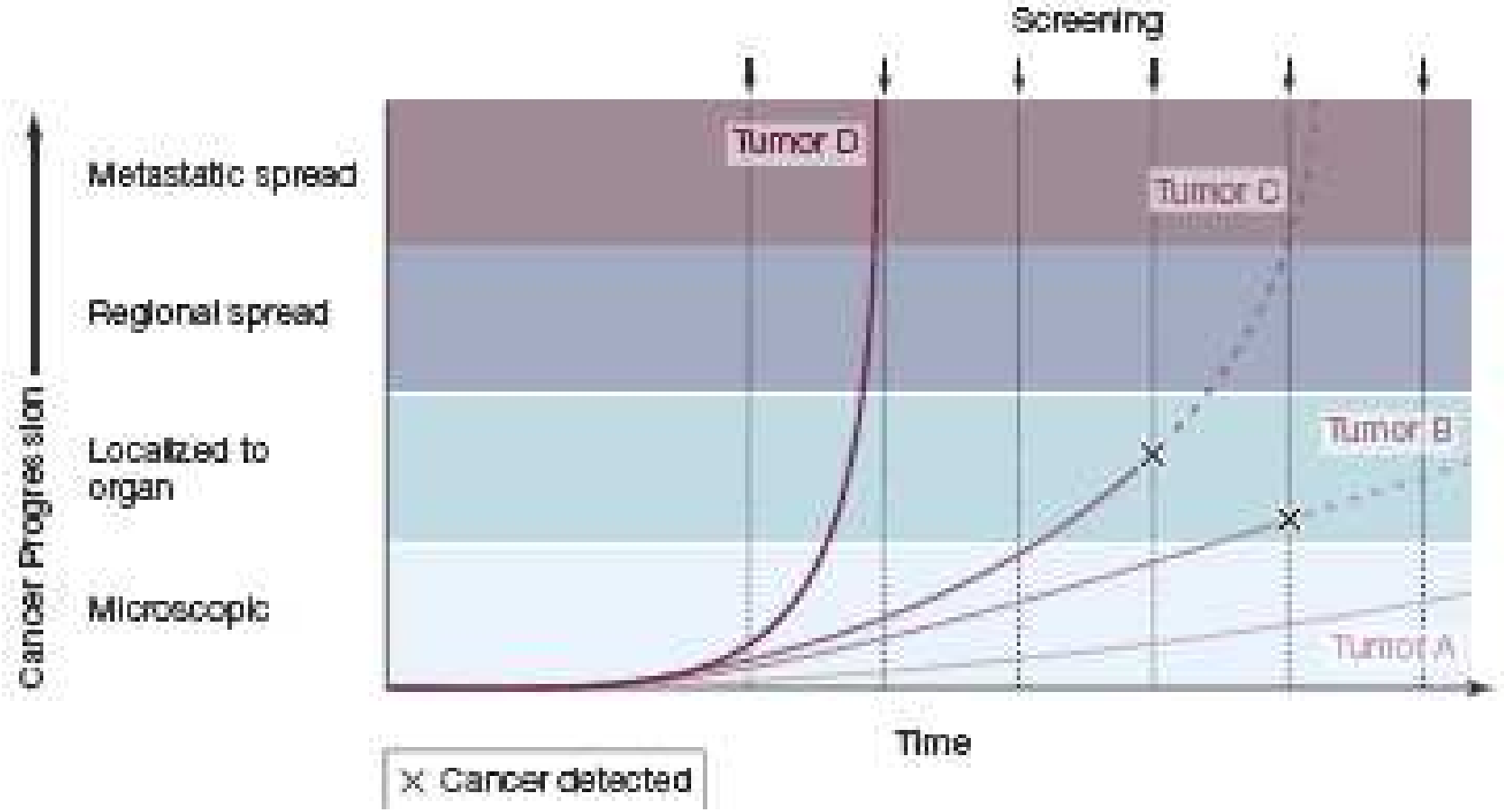
BREAST CANCER AND PROSTATE cancer account for 26% of all cancers in the United States, with an estimated 386 560 patients diagnosed annually: 194 280 for breast cancer and 192 280 for prostate cancer[1] For both, there are remarkable differences between outcomes of localized vs advanced disease (breast cancer: 5-year relative survival rates of 98.1%



JAMA. 2009;302(15):1685-1692



JAMA. 2009;302(15):1685-1692



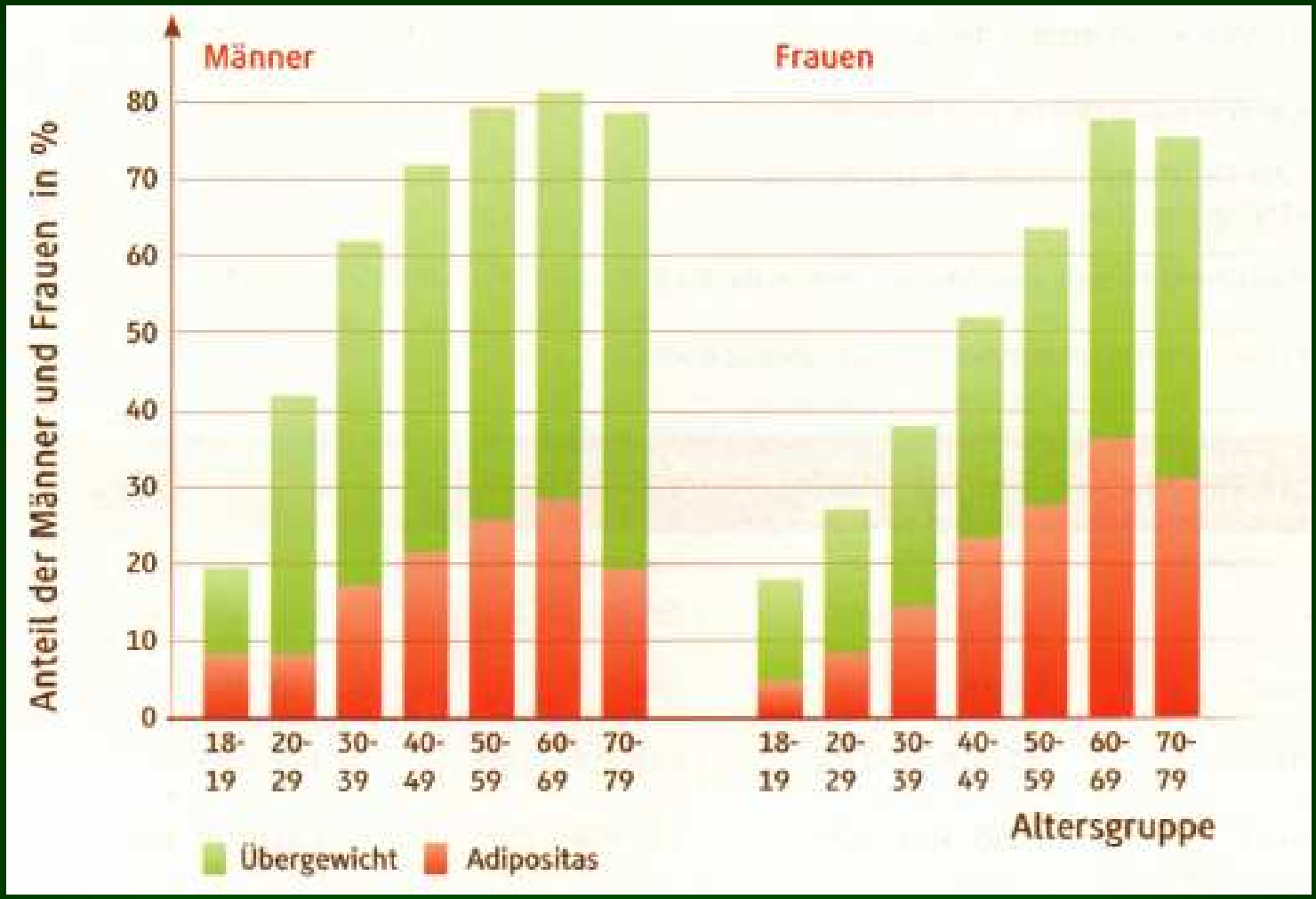
JAMA. 2009;302(15):1685-1692

Altersgruppe (Jahre)	Gesamtzahl der Frauen (n = 110)	Zahl der Frauen mit Brustkrebs (n = 22)	Zahl der Frauen mit atypischen Läsionen (n = 8)
20 - 29	23	0	1
30 - 39	36	3 (8 %)	2
40 - 49	33	13 (39 %)	4
50 - 54	18	6 (33 %)	1

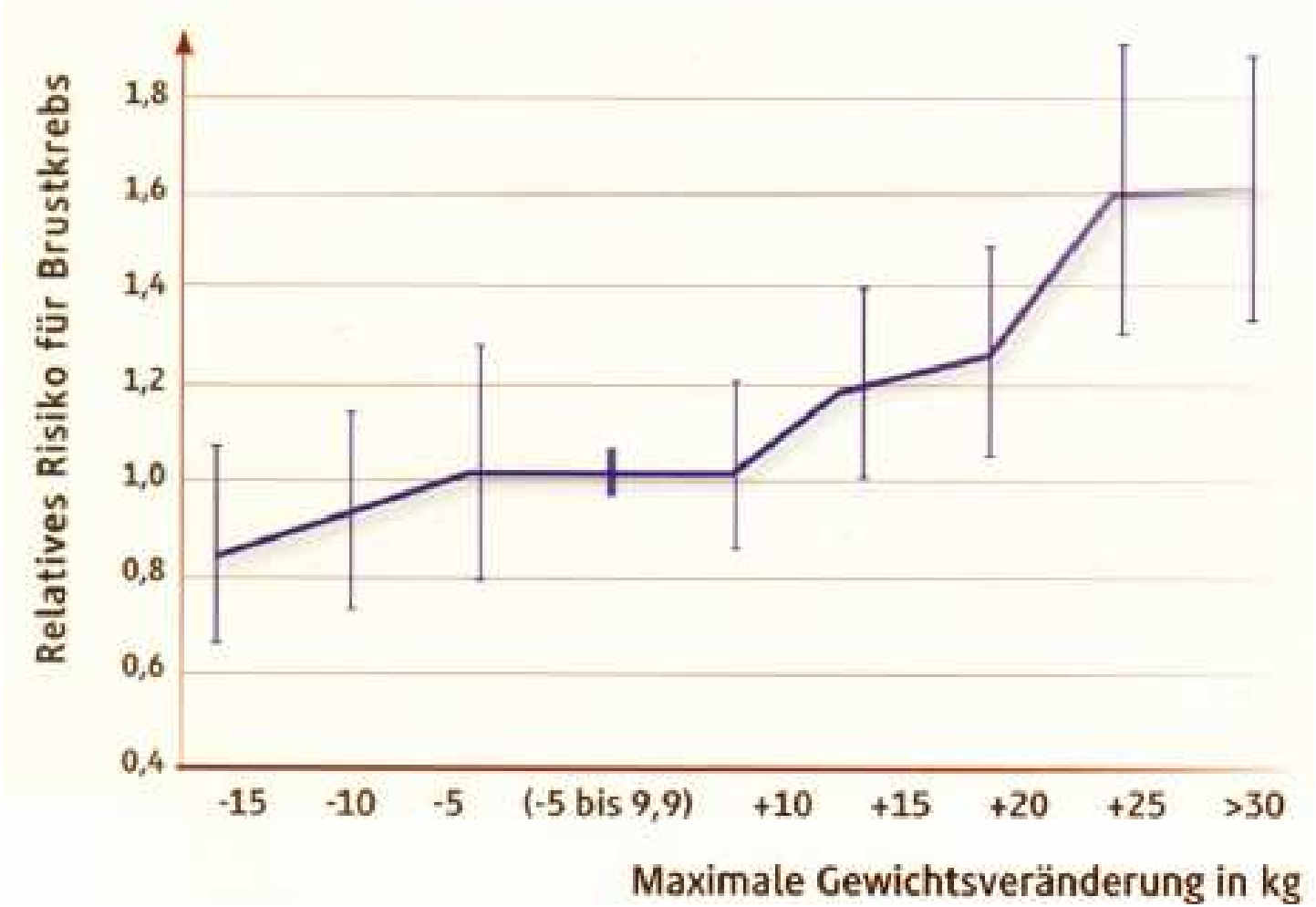
Gerichtsmedizinische Autopsie von radiologisch okkulten Malignome.
Nach Nielsen et al 1987

at a young age (for which surgical prophylaxis reduces absolute risk by more than 40%-70%).[61-63] Chemoprevention may also be an alternative to surgical excision and radiation for minimal-risk cancers.[64]

JAMA. 2009;302(15):1685-1692

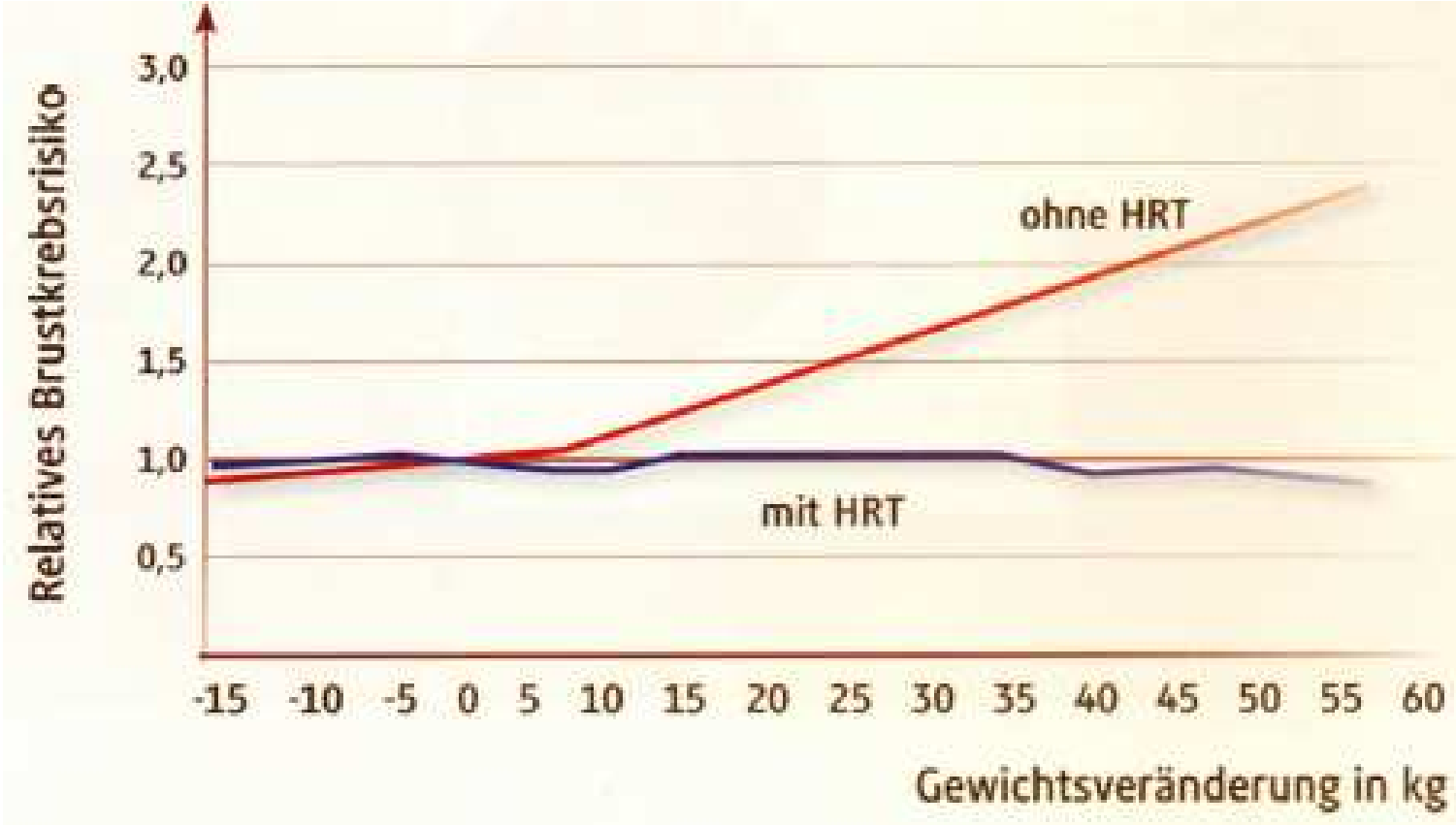


DER PRIVATARZT Medizin & Management
GYNÄKOLOGIE Ausgabe 1 | Februar 2011



Relatives Brustkrebsrisiko postmenopausaler Frauen in Abhängigkeit von der Max. Gewichtszunahme in der Prämenopause nach Trentham Dietz 2000

DER PRIVATARZT Medizin & Management GYNÄKOLOGIE Ausgabe 1 | Februar 2011



Relatives Brustkrebsrisiko der Frauen in der Postmenopause in Abhängigkeit Von der Gewichtszunahme seit dem 18. Lebensjahr; nach Ahn et al 2007

Prävention des Mammakarzinoms (Teil I)

BEI ADIPÖSEN POSTMENOPAUSALEN FRAUEN MINDERT EINE HRT DAS BRUSTKREBSRISIKO

Marika Ehrlich und Herbert Kuhl

DER PRIVATARZT Medizin & Management GYNÄKOLOGIE *Ausgabe 1 | Februar 2011*

BMI (kg / m²)	Relatives Risiko (ohne HRT)	Relatives Risiko (mit HRT oder früherer HRT)
< 22,6	1,00 (Referenz)	1,00 (Referenz)
22,6 - 24,9	1,52	0,89
24,9 - 27,4	1,40	0,86
27,4 - 31,1	1,70	0,92
> 31,1	2,52	0,96

Adipositas, HRT und Brustkrebsrisiko
Nach Morimoto et al 2002 Observationsstudie

BMI (kg / m²)	**Relatives Risiko (ohne HRT)**	**Relatives Risiko (mit HRT oder früherer HRT)**
< 22,6	1,00 (Referenz)	1,00 (Referenz)
22,6 - 24,9	1,52	0,89
24,9 - 27,4	1,4	0,86
27,4 - 31,1	1,7	0,92
> 31,1	2,52	0,96

Der Privatarzt, Gynäkologie, Ausgabe 1 / Februar 2011

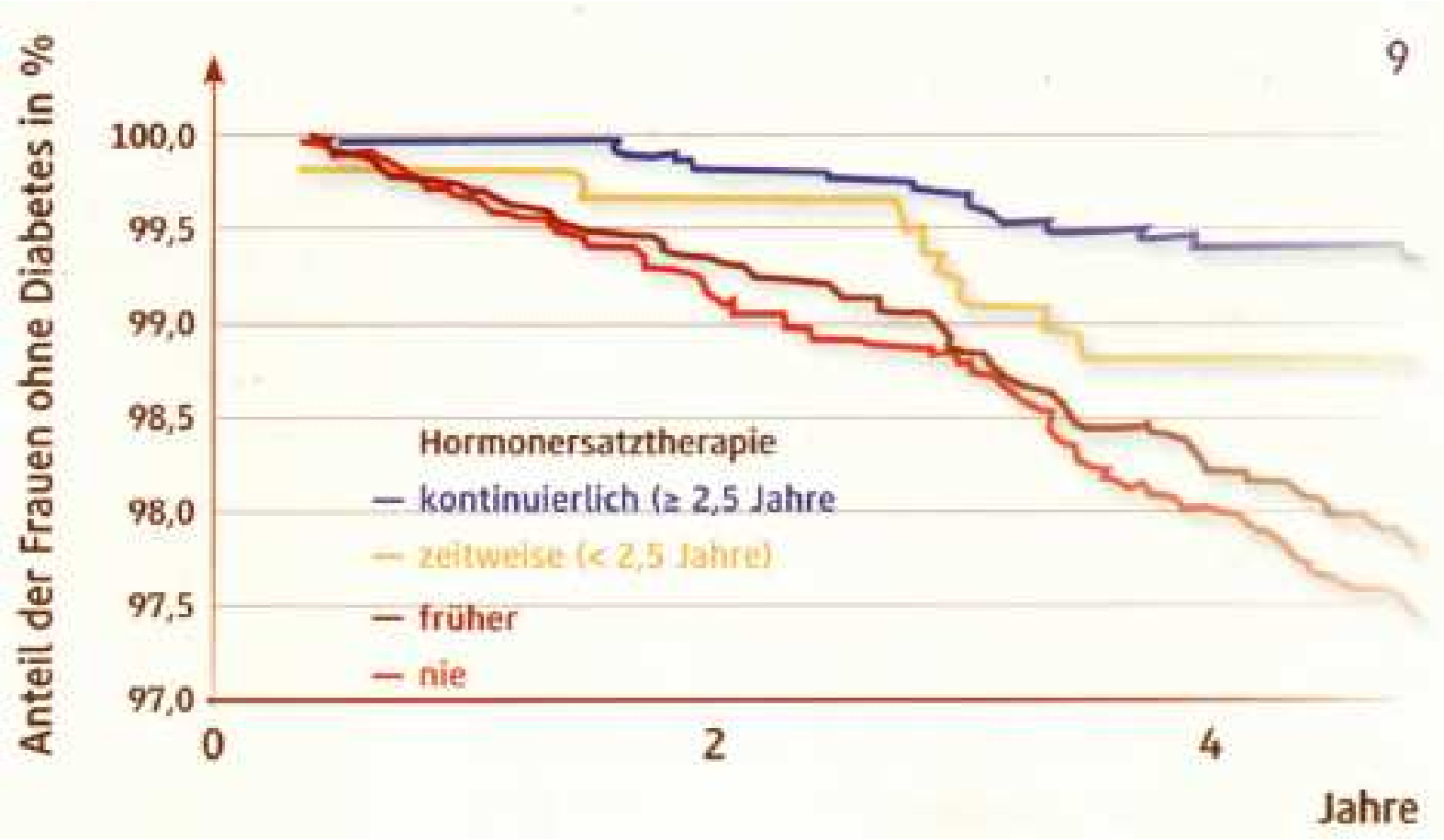
% Körperfett	Relatives Risiko (ohne HRT)	Relatives Risiko (mit HRT)
< 27,0	1,00 (Referenz)	1,00 (Referenz)
27,0 - 29,9	1,94	0,95
30,0 - 32,9	2,57	0,71
33,0 - 36,0	2,29	0,69
> 36,0	3,41	1,00

Adipositas, HRT und Brustkrebs
Prospektive Kohortenstudie mit 12 000 posstmenopausalen Frauen
Nach Lehman et al. 2003

DER PRIVATARZT Medizin & Management GYNÄKOLOGIE
Ausgabe 1 | Februar 2011

% Körperfett	Relatives Risiko (ohne HRT)	Relatives Risiko (mit HRT)
< 27,0	1,00 (Referenz)	1,00 (Referenz)
27,0 - 29,9	1,94	0,95
30,0 - 32,9	2,57	0,71
33,0 - 36,0	2,29	0,69
> 36,0	3,41	1

Der Privatarzt, Gynäkologie, Ausgabe 1 / Februar 2011



Protektion postmenopausaler Frauen vor einem Diabetes II durch HRT
Prospektive Kohortenstudie an 8483 Frauen; nach Pentti et al 2009

Effects of Conjugated Equine Estrogens on Breast Cancer and Mammography Screening in Postmenopausal Women With Hysterectomy

Marcia L. Stefanick, PhD
Garnet L. Anderson, PhD
Karen L. Margolis, MD, MPH
Susan L. Hendrix, DO
Rebecca J. Rodabough, MS
Electra D. Paskett, PhD
Dorothy S. Lane, MD, MPH
F. Allan Hubbell, MD, MSPH
Annlouise R. Assaf, PhD
Gloria E. Sarto, MD
Robert S. Schenken, MD
Shagufta Yasmeen, MD
Lawrence Lessin, MD
Rowan T. Chlebowski, MD, PhD
for the WHI Investigators

Context The Women's Health Initiative Estrogen-Alone trial comparing conjugated equine estrogens (CEE) with placebo was stopped early because of an increased stroke incidence and no reduction in risk of coronary heart disease. Preliminary results suggesting possible reduction in breast cancers warranted more detailed analysis.

Objective To determine the effects of CEE on breast cancers and mammographic findings.

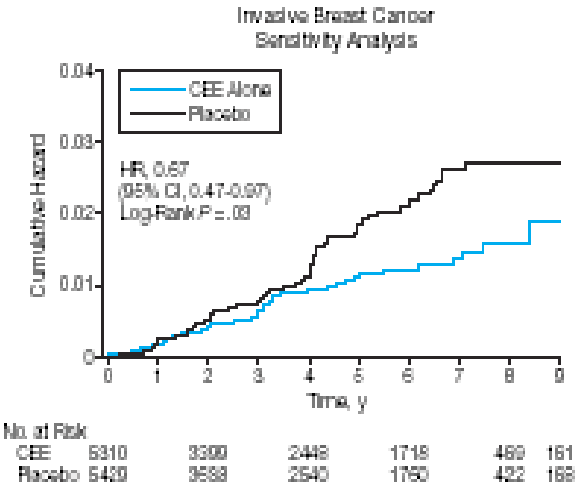
Design, Setting, and Participants Following breast cancer risk assessment, 10739 postmenopausal women aged 50 to 79 years with prior hysterectomy were randomized to CEE or placebo at 40 US clinical centers from 1993 through 1998. Mammography screenings and clinical breast examinations were performed at baseline and annually. All breast cancers diagnosed through February 29, 2004, are included.

Intervention A dose of 0.625 mg/d of CEE or an identical-appearing placebo.

Main Outcome Measures Breast cancer incidence, tumor characteristics, and mammogram findings.

Results After a mean (SD) follow-up of 7.1 (1.6) years, the invasive breast cancer hazard ratio (HR) for women assigned to CEE vs placebo was 0.80 (95% confidence interval [CI], 0.62-1.04; $P = .09$) with annualized rates of 0.28% (104 cases in the CEE group) and 0.34% (133 cases in the placebo group). In exploratory analyses, ductal

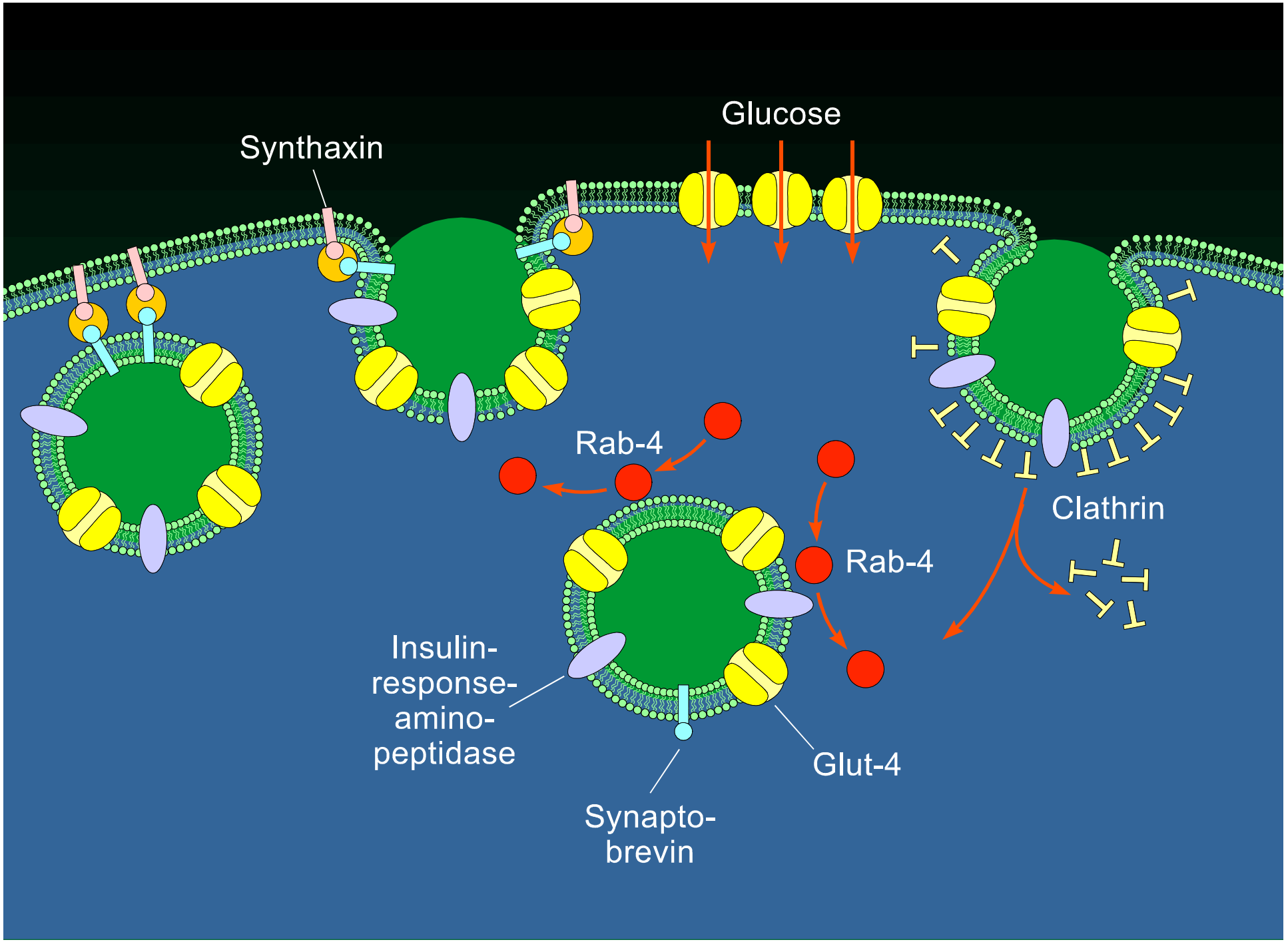
Figure 2. Cumulative Hazard for Invasive Breast Cancer: Sensitivity Analysis



Participants with less than 80% adherence to study medications were censored 6 months after their first episode of nonadherence. CEE indicates conjugated equine estrogens; CI, confidence interval; HR, hazard ratio.

- Das erhöhte Insulin regt die Zellteilung an und fördert die Karzinomentwicklung.
- Das erhöhte Insulin stimuliert die Aromataseaktivität im Fettgewebe.
- Das erhöhte Insulin reduziert das Sexualhormon-bindende Globulin (SHBG) und erhöht das freie Estradiol.
- Das erhöhte Insulin geht mit einer Erhöhung auch des freien Insulin-like Growth Factor 1 (IGF-1) einher.
- Erhöhte Freisetzung von Leptin aus dem viszeralen Fettgewebe, welches das Karzinomwachstum und die Angiogenese stimuliert.
- Reduzierte Freisetzung von Adiponektin, welches das Karzinomwachstum und die Angiogenese hemmt.
- Die Freisetzung von inflammatorischen Zytokinen ist erhöht.

Der Privatarzt, Gynäkologie, Ausgabe 1 / Februar 2011


Glucose
Synthaxin
Rab-4
Rab-4
Clathrin
Insulin-
response-
amino-
peptidase
Glut-4
Synapto-
brevin

Risikofaktor		Relatives Risiko
Serum-Insulin	niedrig vs. hoch	1 : 2,9 (+ 190 %)
Körpergewicht	normal vs. Adipositas	1 : 2,5 (+ 150 %)
Serum-Lipide	normal vs. erhöht	1 : 1,6 (+ 60 %)
Alkoholkonsum	kein vs. ≥ 20 g täglich	1 : 1,3 (+ 30 %)
Rauchen	nie vs. 10 Zigaretten täglich	1 : 1,3 (+ 30 %)
Körperliche Aktivität	aktiv vs. inaktiv	1 : 1,2 (+ 20 %)

Modifizierbare Lêbensstil Risikofaktoren for die Entwicklung eines Mammakarzinoms

DER PRIVATARZT Medizin & Management GYNÄKOLOGIE Ausgabe 1 | Februar 2011

Risikofaktor		**Relatives Risiko**
Serum-Insulin	niedrig vs. hoch	1 : 2,9 (+ 190 %)
Körpergewicht	normal vs. Adipositas	1 : 2,5 (+ 150 %)
Serum-Lipide	normal vs. erhöht	1 : 1,6 (+ 60 %)
Alkoholkonsum	kein vs. ≥ 20 g täglich	1 : 1,3 (+ 30 %)
Rauchen	nie vs. 10 Zigaretten täglich	1 : 1,3 (+ 30 %)
Körperliche Aktivität	aktiv vs. inaktiv	1 : 1,2 (+ 20 %)

Der Privatarzt, Gynäkologie, Ausgabe 1 / Februar 2011

Insulin-Lowering Effects of Metformin in Women with Early Breast Cancer

Pamela J. Goodwin,[1,2,3,4] Kathleen I. Pritchard,[5,6] Marguerite Ennis,[7] Mark Clemons,[3,8] Margaret Graham,[4] I. George Fantus[4,9]

Conclusion: Metformin significantly lowers insulin levels, and it improves insulin resistance in nondiabetic women with breast cancer. A phase III randomized trial to evaluate its effects on breast cancer outcomes is recommended.

RESEARCH POINTERS

Metformin and reduced risk of cancer in diabetic patients

Josie M M Evans, Louise A Donnelly, Alistair M Emslie-Smith, Dario R Alessi, Andrew D Morris

Review Article

Mechanisms of Disease

Production and Actions of Estrogens

Christian J. Gruber, M.D., Walter Tschugguel, M.D., Christian Schneeberger, Ph.D., and Johannes C. Huber, M.D., Ph.D.

tase monooxygenase enzyme complex that is present in the smooth endoplasmic reticulum and functions as a demethylase. In three consecutive hydroxylating reactions, estrone and estradiol are formed from their obligatory precursors androstenedione and testosterone, respectively (Fig. 1). The final hydroxylating step in aromatization does not require enzymatic action and is not product sensitive.

Several plant compounds have structural and functional similarities to estrogens and are therefore referred to as phytoestrogens (Fig. 1). Genistein and daidzein are isoflavonoids found in soybeans and clo-

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

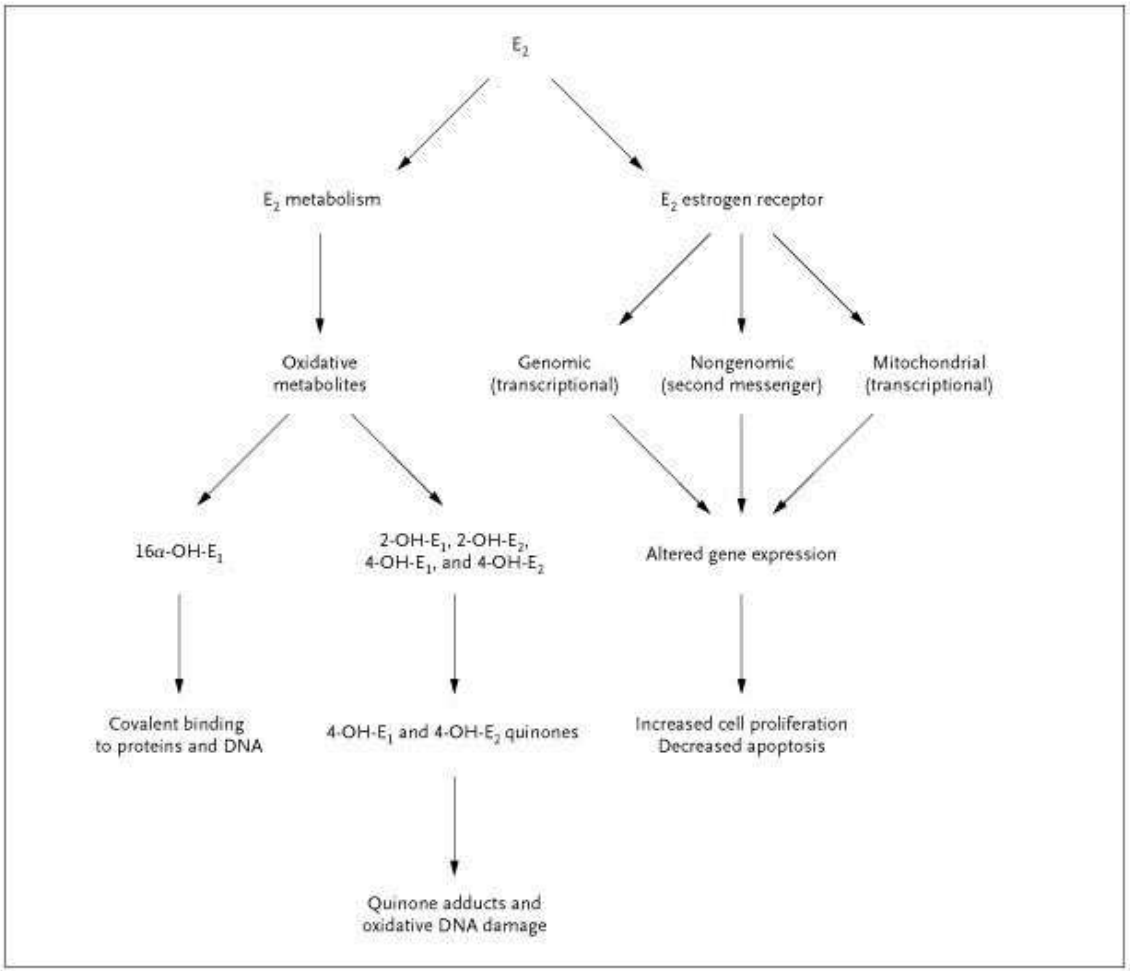
MECHANISMS OF DISEASE

Estrogen Carcinogenesis in Breast Cancer

James D. Yager, Ph.D., and Nancy E. Davidson, M.D.

IN THIS ARTICLE, WE REVIEW RECENT FINDINGS RELATED TO ESTROGEN EXposure and the risk of breast cancer, the mechanisms that may be involved, and the clinical implications of these findings. The weight of evidence indicates that exposure to estrogen is an important determinant of the risk of breast cancer. The mechanisms of carcinogenesis in the breast caused by estrogen include the metabolism of estrogen to genotoxic, mutagenic metabolites and the stimulation of tissue growth. Together, these processes cause initiation, promotion, and progression of car-

N Engl J Med 2006;354:270-82.

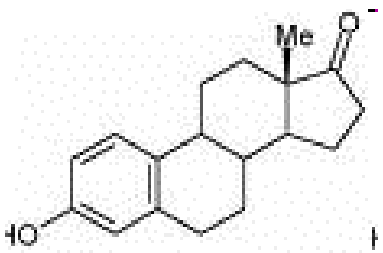


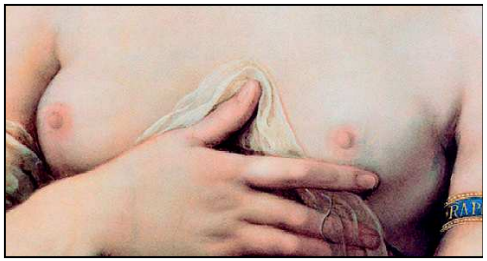
Chapter 4: Estrogens as Endogenous Genotoxic Agents—DNA Adducts and Mutations

Ercole Cavalieri, Krystyna Frenkel, Joachim G. Liehr, Eleanor Rogan, Deodutta Roy

Glutathione Conjugates

Stable Adducts

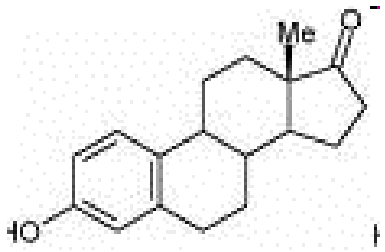




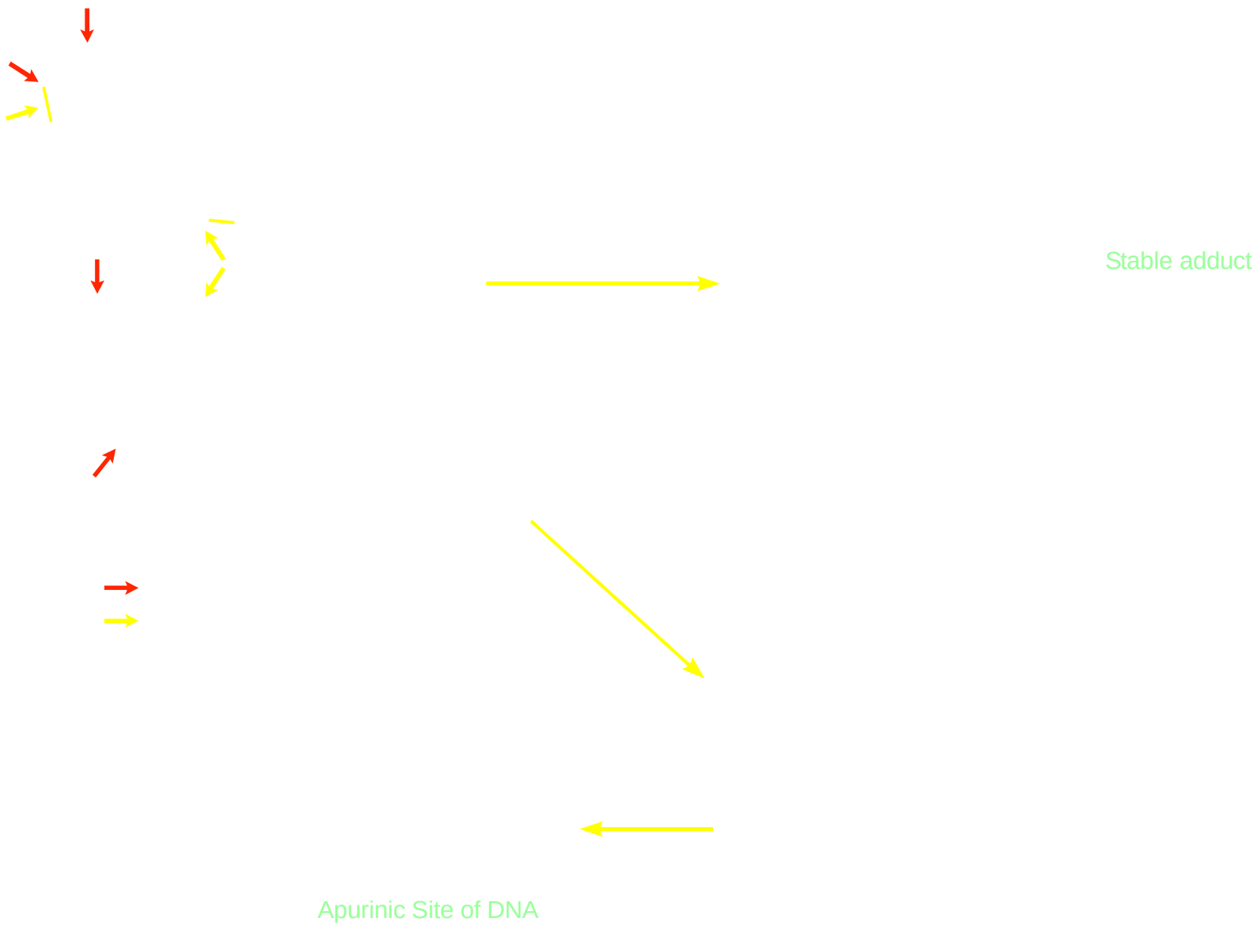
Chapter 4: Estrogens as Endogenous Genotoxic Agents—DNA Adducts and Mutations

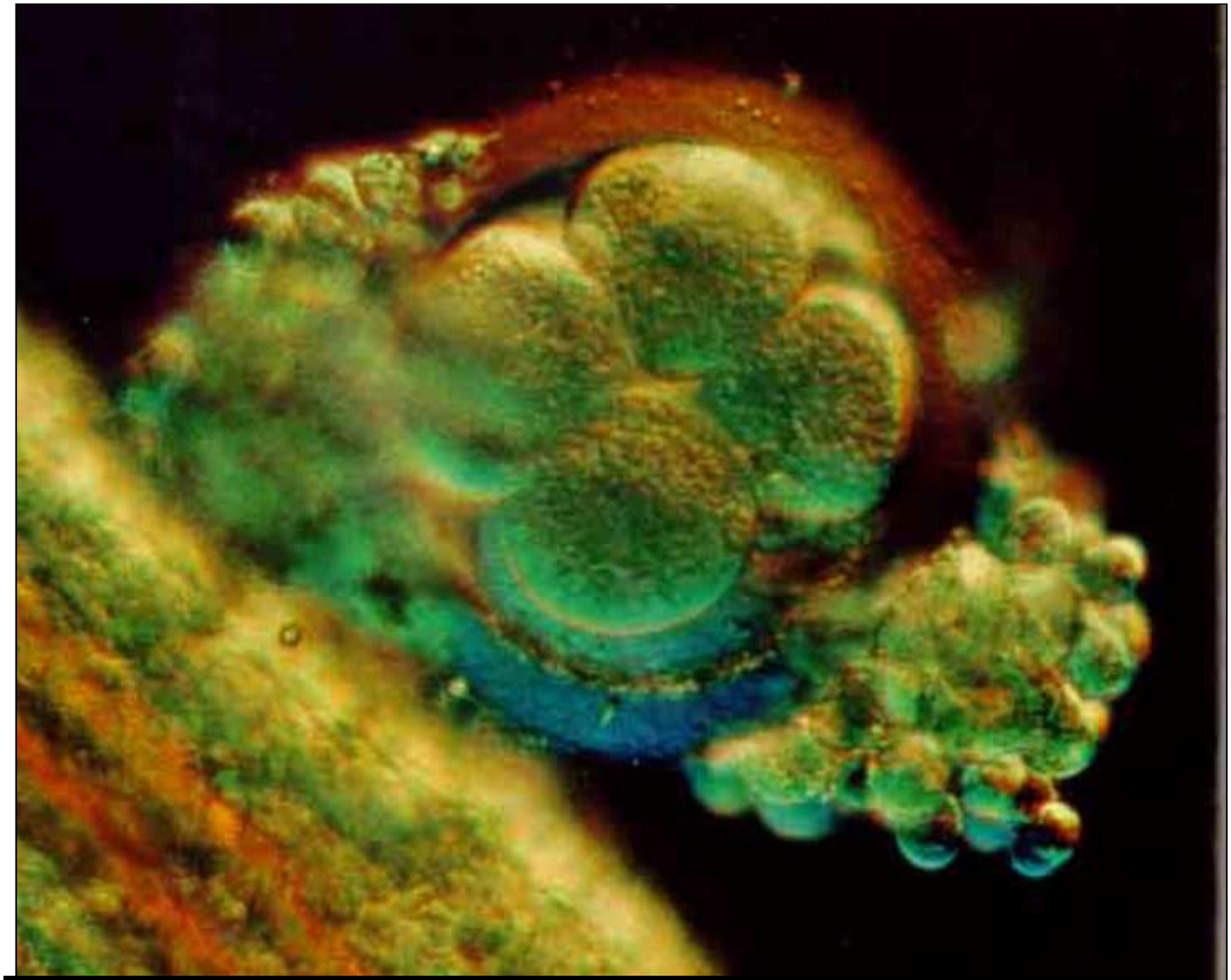
Ercole Cavalieri, Krystyna Frenkel, Joachim G. Liehr, Eleanor Rogan, Deodutta Roy

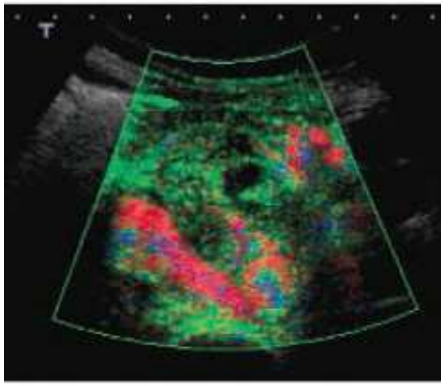
Glutathione Conjugates

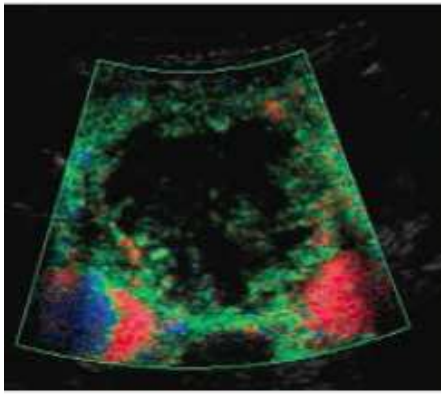


Depurinating Adducts


Stable adduct
Apurinic Site of DNA
Depurinating adduct







Paria, B.C., et. Al
Embryo Implantation Requires Estrogen-Directed Uterine Preparation and Catecholestrogen-Mediated Embryonic Activation
Advances in Pharmacology, Vol. 42, pp. 840-842

KARDIOPROTEKTIV
ANTIMITOTISCH
ANTIAGIOGENESE

KARDIOPROTEKTIV
ANTIANGIOGENESE
ONKOPROTEKTIV

CYP 1A1

COMT

CYP 1A1
CYP 1B1

COMT

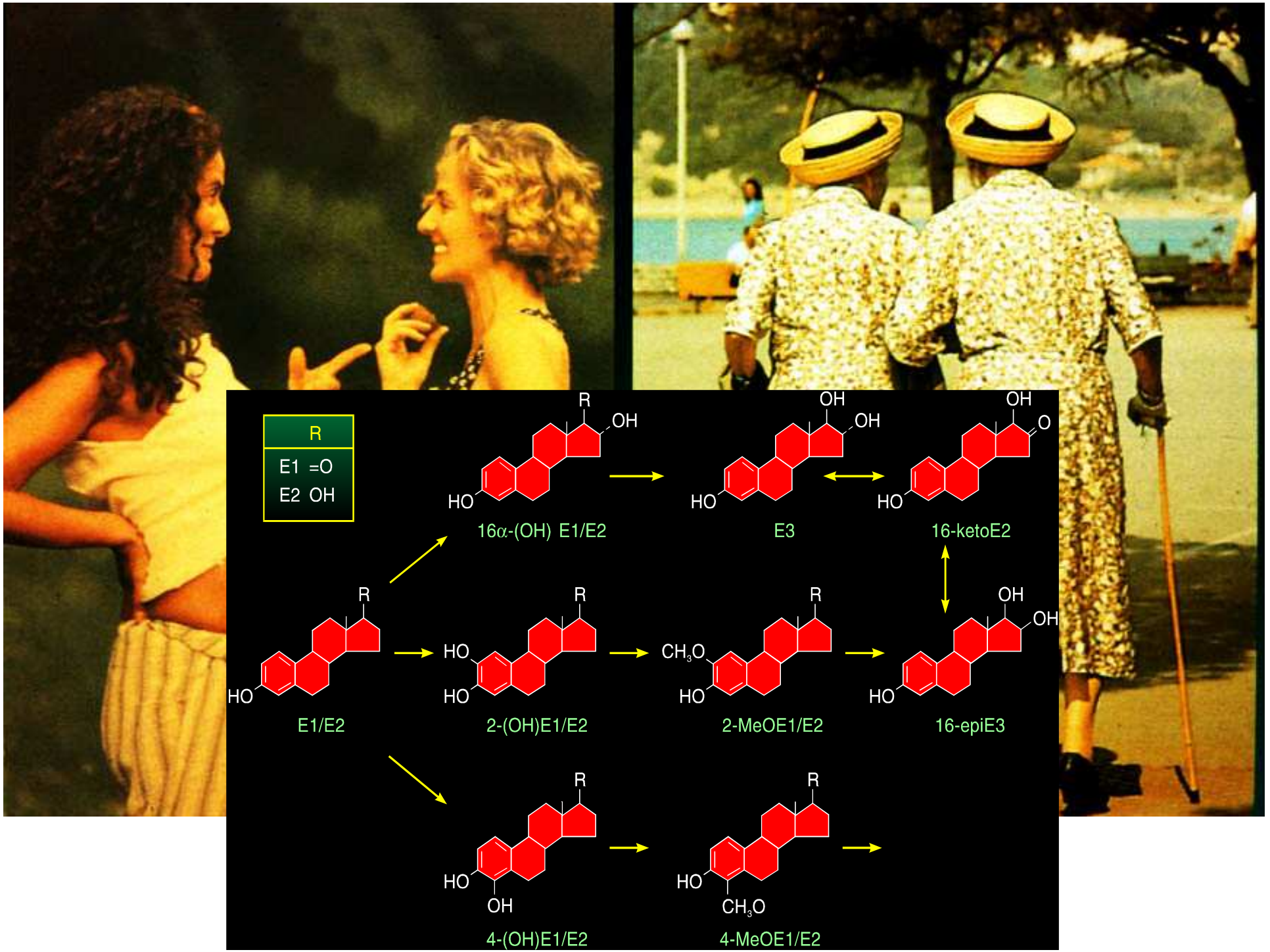
Pharmacogenetics and Regulation of Human Cytochrome *P*450 1B1: Implications in Hormone-Mediated Tumor Metabolism and a Novel Target for Therapeutic Intervention

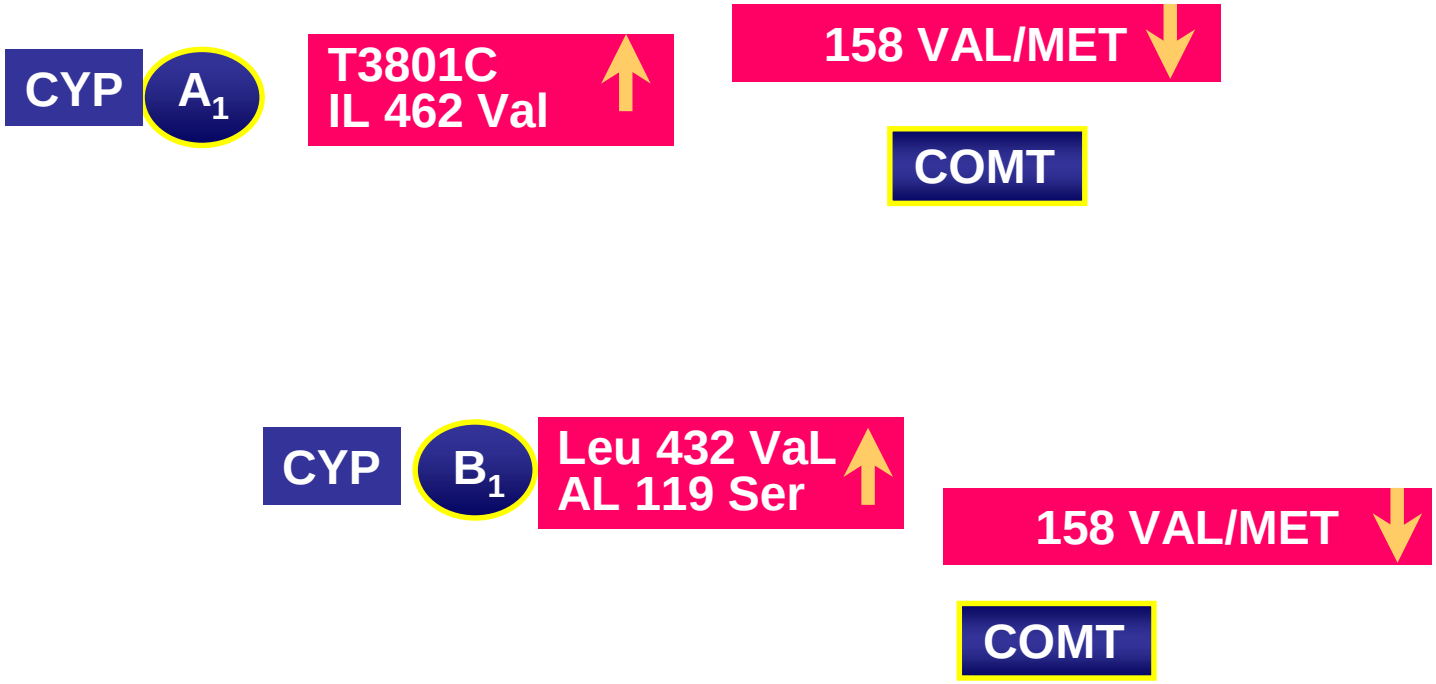
Tristan M. Sissung, Douglas K. Price, Alex Sparreboom, and William D. Figg

Clinical Pharmacology Research Core and Cancer Therapeutics Branch, National Cancer Institute, Bethesda, Maryland

Implantations-
Mitose-
Angiogenese
induzierend

GST


R
E1 =O
E2 OH
16α-(OH) E1/E2
E3
16-ketoE2
E1/E2
2-(OH)E1/E2
2-MeOE1/E2
16-epiE3
4-(OH)E1/E2
4-MeOE1/E2


CYP
A1
T3801C
IL 462 Val
158 VAL/MET
COMT
CYP
B1
Leu 432 VaL
AL 119 Ser
158 VAL/MET
COMT

CANCER CHEMOPREVENTION WITH DIETARY PHYTOCHEMICALS

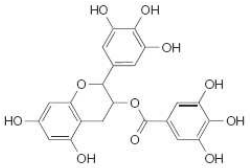
Young-Joon Surh

Chemoprevention refers to the use of agents to inhibit, reverse or retard tumorigenesis. Numerous phytochemicals derived from edible plants have been reported to interfere with a specific stage of the carcinogenic process. Many mechanisms have been shown to account for the anticarcinogenic actions of dietary constituents, but attention has recently been focused on intracellular-signalling cascades as common molecular targets for various chemopreventive phytochemicals.

Cancer is a growing health problem around the world — particularly with the steady rise in life expectancy, increasing urbanization and the subsequent changes in environmental conditions, including lifestyle. According to a recent report by the World Health Organization

A wide array of substances derived from the diet have been found to stimulate the development, growth and spread of tumours in experimental animals, and to transform normal cells into malignant ones. These are regarded as suspected human carcinogens.

BARBITURATE
INDOL – 3 – CARBINOL
EPIGALLOCATECHIN



Epigallocatechin-3-gallate

RETINOIDE
CHOLECHALCIFEROL
HESPERDINE

CYP 1A1

FOLAT

COMT

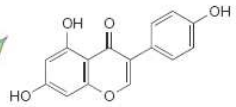
CYP 1A1
CYP 1B1

COMT

RETINOIDE
CHOLECHALCIFEROL
HESPERDINE

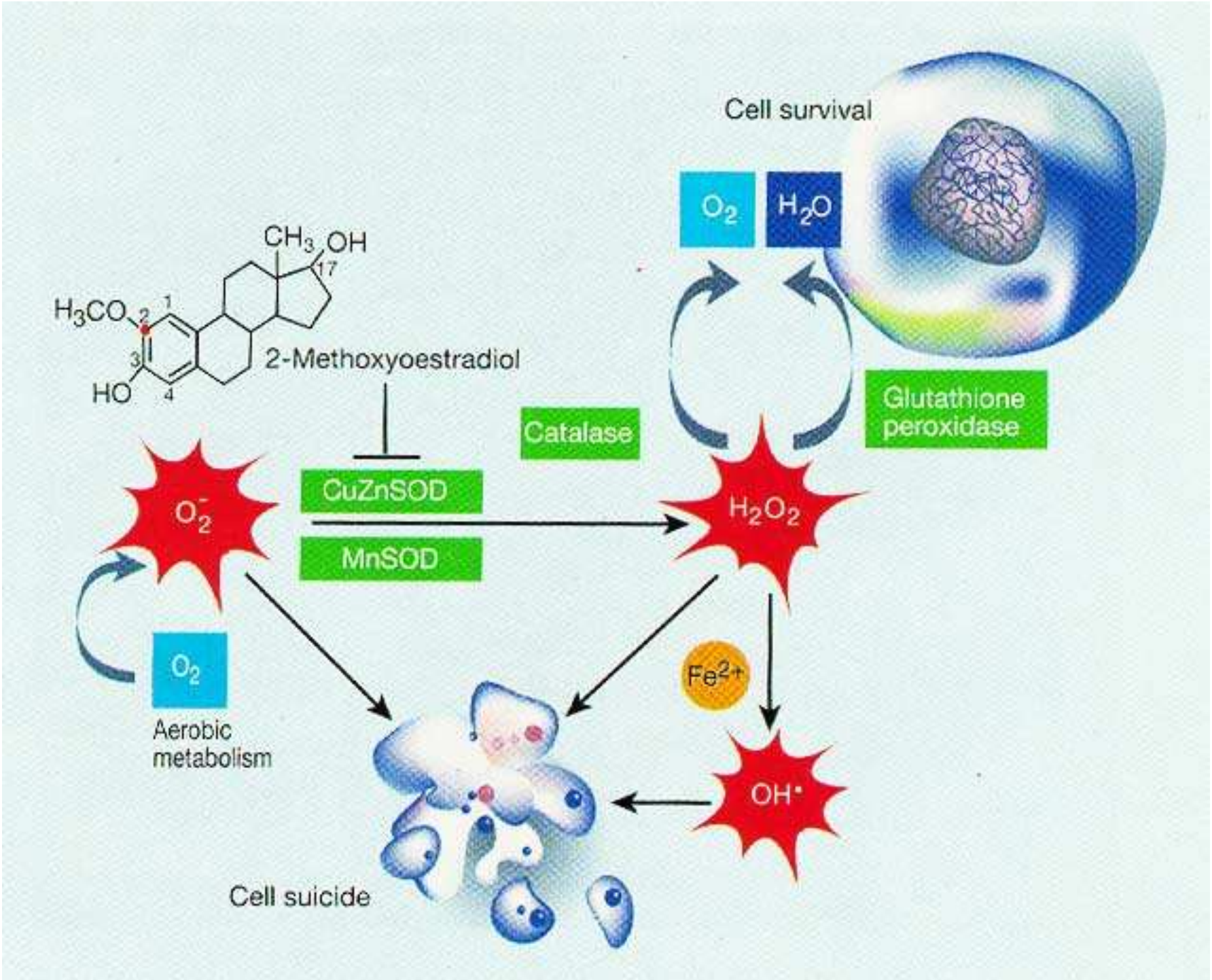
GST ← SELEN

ISOFLA-VONE



Genistein

www.nature.com/reviews/cancer


Cell survival
O_2
H_2O
CH_3 OH
17
H_3CO
2
1
3
HO
4
2-Methoxyoestradiol
Catalase
Glutathione peroxidase
O_2^-
CuZnSOD
MnSOD
H_2O_2
O_2
Aerobic metabolism
Fe^{2+}
$OH^\bullet$
Cell suicide

VOLUME 25 · NUMBER 6 · FEBRUARY 20 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Plasma Phytoestrogens and Subsequent Breast Cancer Risk

Martijn Verheus, Carla H. van Gils, Lital Keinan-Boker, Philip B. Grace, Sheila A. Bingham, and Petra H.M. Peeters

From the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands; Israel Center for Disease Control, Ministry of Health, and School of Public Health, University of Haifa, Haifa, Israel; Horseracing Forensic Laboratory Ltd, Fordham; and the Medical Research Council Dunn Human Nutrition Unit, Cambridge, United Kingdom.

ABSTRACT

Purpose

Phytoestrogens are plant compounds that are structurally and functionally similar to mammalian estrogens. By competing for estrogen receptors, phytoestrogens possibly inhibit binding of the more potent endogenous estrogens and decrease their potential effects on breast cancer risk. We investigated the association between plasma phytoestrogen levels and breast cancer risk in a prospective manner.

Published Ahead of Print on March 3, 2008 as 10.1200/JCO.2007.13.9964
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2007.13.9964
VOLUME 26 · NUMBER 10 · APRIL 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Plasma Isoflavone Level and Subsequent Risk of Breast Cancer Among Japanese Women: A Nested Case-Control Study From the Japan Public Health Center-Based Prospective Study Group

Motoki Iwasaki, Manami Inoue, Tetsuya Otani, Shizuka Sasazuki, Norie Kurahashi, Tsutomu Miura, Seiichiro Yamamoto, and Shoichiro Tsugane

From the Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center; Department of Sport and Exercise Nutrition, School of Physical Education, Sendai University; and the Cancer Information Services and Surveillance Division, Center for Cancer

ABSTRACT

Purpose

Because they have large variations in consumption, Asian countries are suitable settings for studies of the effect of relatively high-dose isoflavone intake on breast cancer risk. Nevertheless, no prospective study from Asia has assessed blood or urine levels as biomarkers of isoflavone intake.

MODERN TRENDS

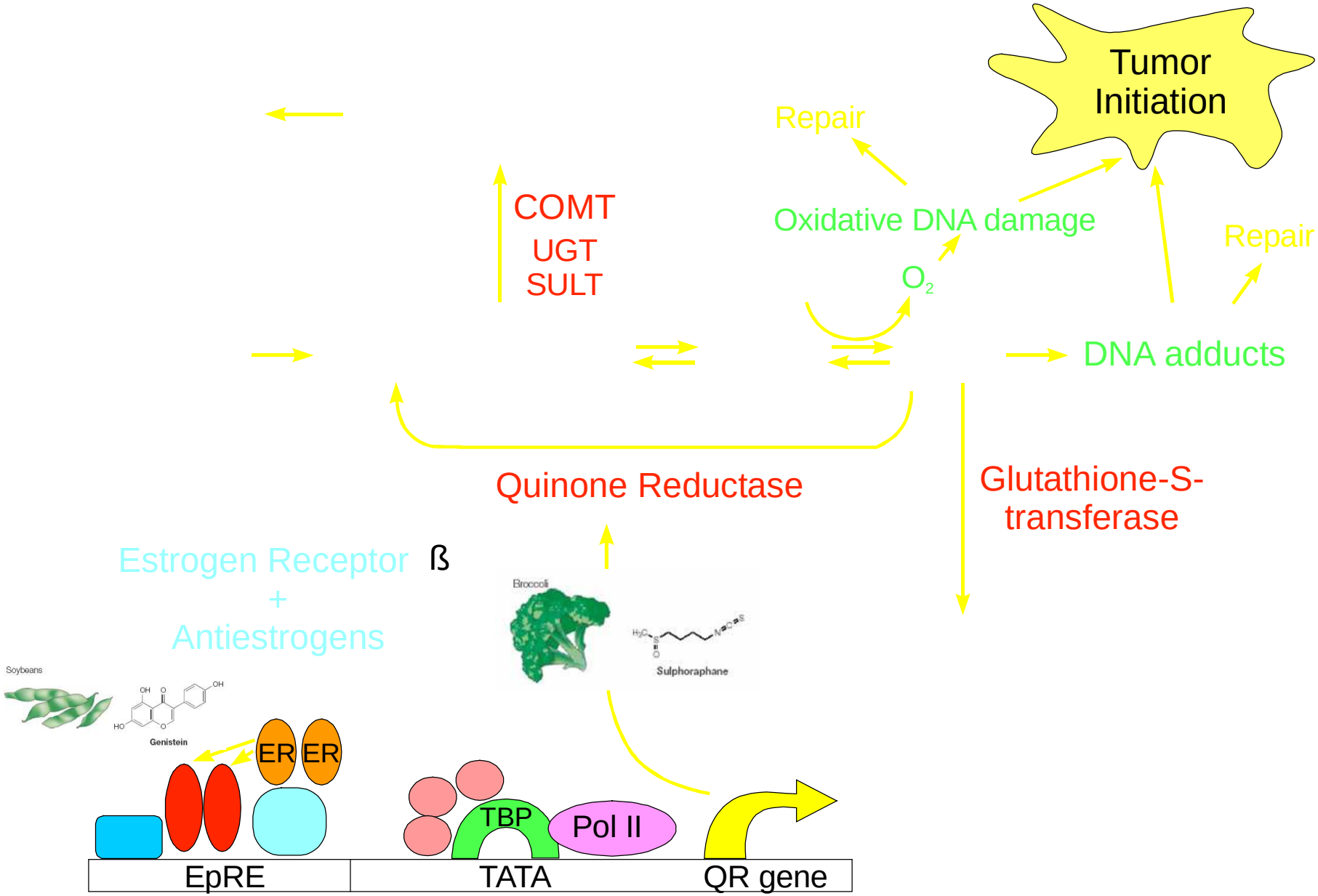
Edward E. Wallach, M.D.
Associate Editor

Phytoestrogens in clinical practice: a review of the literature

Clemens B. Tempfer, M.D.,[a] *Eva-Katrin Bentz, M.D.,*[a] *Sepp Leodolter, M.D.,*[a] *Georg Tscherne, M.D.,*[b] *Ferdinand Reuss, M.D.,*[b] *Heide S. Cross, Ph.D.,*[c] *and Johannes C. Huber, M.D., Ph.D.*[a]

[a] Department of Obstetrics and Gynecology, Medical University of Vienna, Vienna; [b] Department of Obstetrics and Gynecology, Medical University of Graz, Graz; and [c] Department of Pathophysiology, Medical University of Vienna, Vienna, Austria

Objective: To review clinical studies assessing the effect of phytoestrogen supplementation on the signs and symptoms of the climacteric syndrome and on the incidence of breast cancer, cardiovascular disease, and skeletal fractures.


Tumor Initiation
Repair
COMT
UGT
SULT
Oxidative DNA damage
O_2
Repair
DNA adducts
Quinone Reductase
Glutathione-S-transferase
Estrogen Receptor ß
+
Antiestrogens
Broccoli
Sulphoraphane
Soybeans
Genistein
ER ER
TBP
Pol II
EpRE
TATA
QR gene

nature genetics

NAD(P)H:quinone oxidoreductase 1 *NQO1*2* genotype (P187S) is a strong prognostic and predictive factor in breast cancer

Rainer Fagerholm[1,17], Barbara Hofstetter[2,17], Johanna Tommiska[1,17], Kirsimari Aaltonen[1,3], Radek Vrtel[2,16], Kirsi Syrjäkoski[4], Anne Kallioniemi[4], Outi Kilpivaara[1], Arto Mannermaa[5,6], Veli-Matti Kosma[5,6], Matti Uusitupa[7], Matti Eskelinen[8], Vesa Kataja[9,10], Kristiina Aittomäki[11], Karl von Smitten[12], Päivi Heikkilä[13], Jiri Lukas[2], Kaija Holli[14], Jirina Bartkova[2], Carl Blomqvist[3,15], Jiri Bartek[2,16] & Heli Nevanlinna[1]

NQO1 guards against oxidative stress and carcinogenesis and stabilizes p53. We find that a homozygous common missense variant (***NQO1*2***, rs1800566(T), NM_000903.2:c.558C>T) that disables NQO1 strongly predicts poor survival among two independent series of women with breast cancer ($P = 0.002$, $N = 1{,}005$; $P = 0.005$, $N = 1{,}162$), an effect particularly evident after anthracycline-based adjuvant chemotherapy with epirubicin ($P = 7.52 \times 10^{-6}$) and in p53-aberrant tumors ($P = 6.15 \times 10^{-5}$). Survival after metastasis was reduced among ***NQO1*2*** homozygotes, further implicating NQO1 deficiency in cancer progression and treatment resistance. Consistently, response to epirubicin was impaired in ***NQO1*2***-homozygous breast carcinoma cells ***in vitro,*** reflecting both p53-linked and p53-independent roles of NQO1. We propose a model of defective anthracycline response in NQO1-deficient breast tumors, along with increased genomic instability promoted by elevated reactive oxygen species (ROS), and suggest that the ***NQO1*** genotype is a prognostic and predictive marker for breast cancer.

ANDROGEN EFFECTS ON FEMALE HEALTH

FERTILITY AND STERILITY®
VOL. 77, NO. 4, SUPPL 4, APRIL 2002

Published by Elsevier Science Inc.
Printed on acid-free paper in U.S.A.

Androgens and mammary growth and neoplasia

Constantine Dimitrakakis, M.D., Jian Zhou, M.D., and Carolyn A. Bondy, M.D.

Developmental Endocrinology Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland

Testosteron → Dihydro-Testosteron → Androstandion

↓

Östradiol

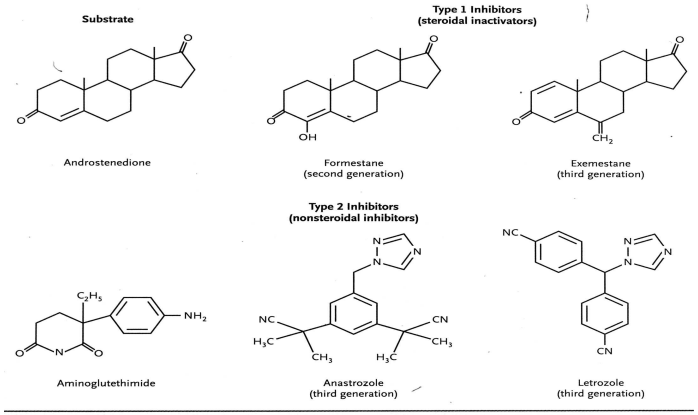


Figure 2. Structures of the Main Aromatase Inhibitors and the Natural Substrate Androstenedione.

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

DRUG THERAPY

Alastair J.J. Wood, M.D., *Editor*

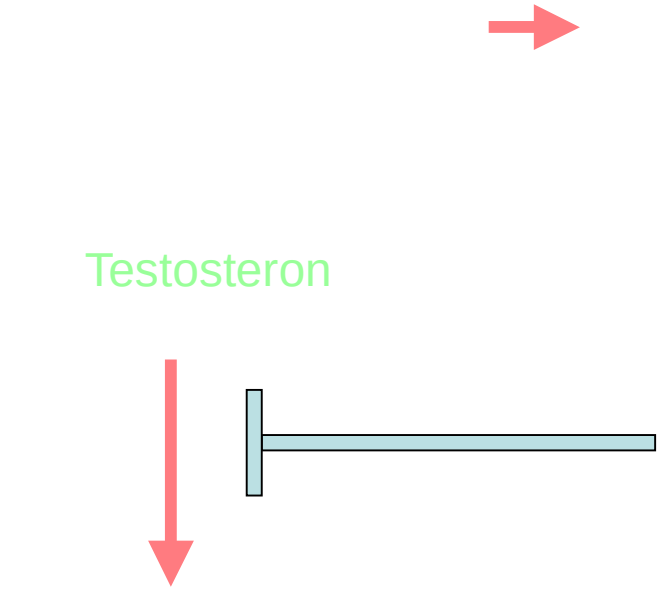
Aromatase Inhibitors in Breast Cancer

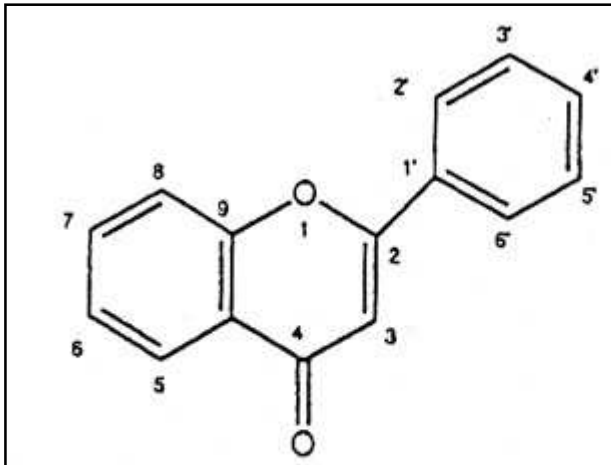
Ian E. Smith, M.D., and Mitch Dowsett, Ph.D.

THE THIRD-GENERATION AROMATASE INHIBITORS PROVIDE NOVEL approaches to the endocrine treatment of breast cancer. These drugs are effectively challenging tamoxifen, the previous gold standard of care,[1-13] for use in postmenopausal patients with estrogen-receptor–positive cancers, who make up the majority of patients with breast cancer. These agents are also being considered for use in chemoprevention, a strategy in which tamoxifen has already been shown to reduce the incidence of breast cancer.[14,15] In this article, we review the current role of aromatase inhibitors and assess their potential for clinical use. Other reviews that may be of interest to specialists are also available.[16,17]

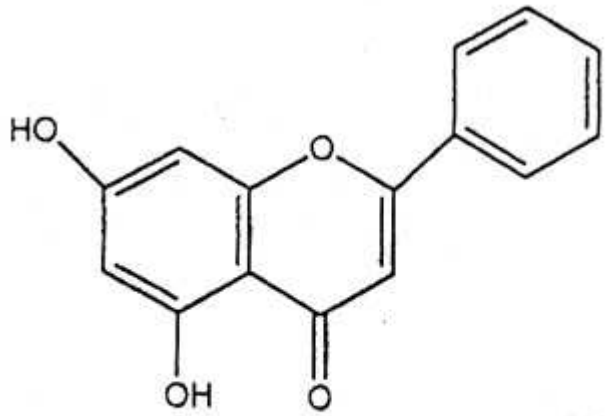
From the Royal Marsden Hospital and Institute of Cancer Research, London. Address reprint requests to Dr. Smith at the Breast Unit, Royal Marsden Hospital, Fulham Rd., London SW3 6JJ, United Kingdom, or at ian.smith@rmh.nthames.nhs.uk.

N Engl J Med 2003;348:2431-42.

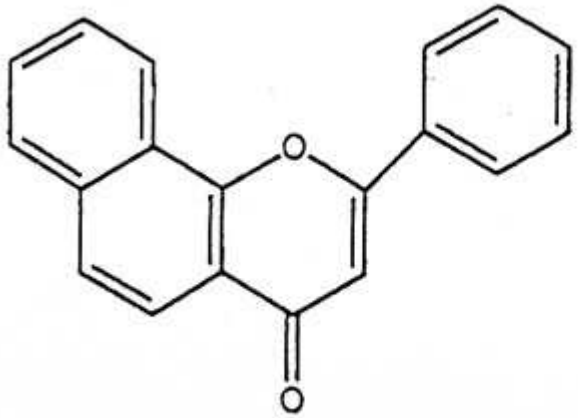




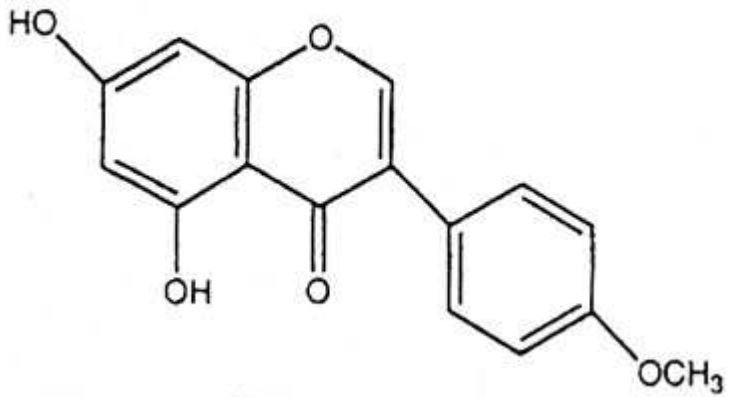
Flavone



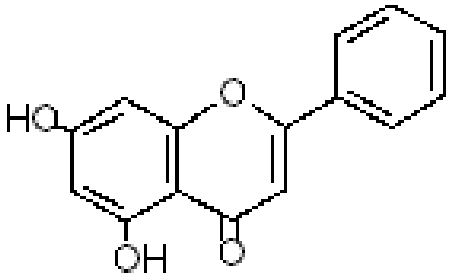
Chrysin



ANF



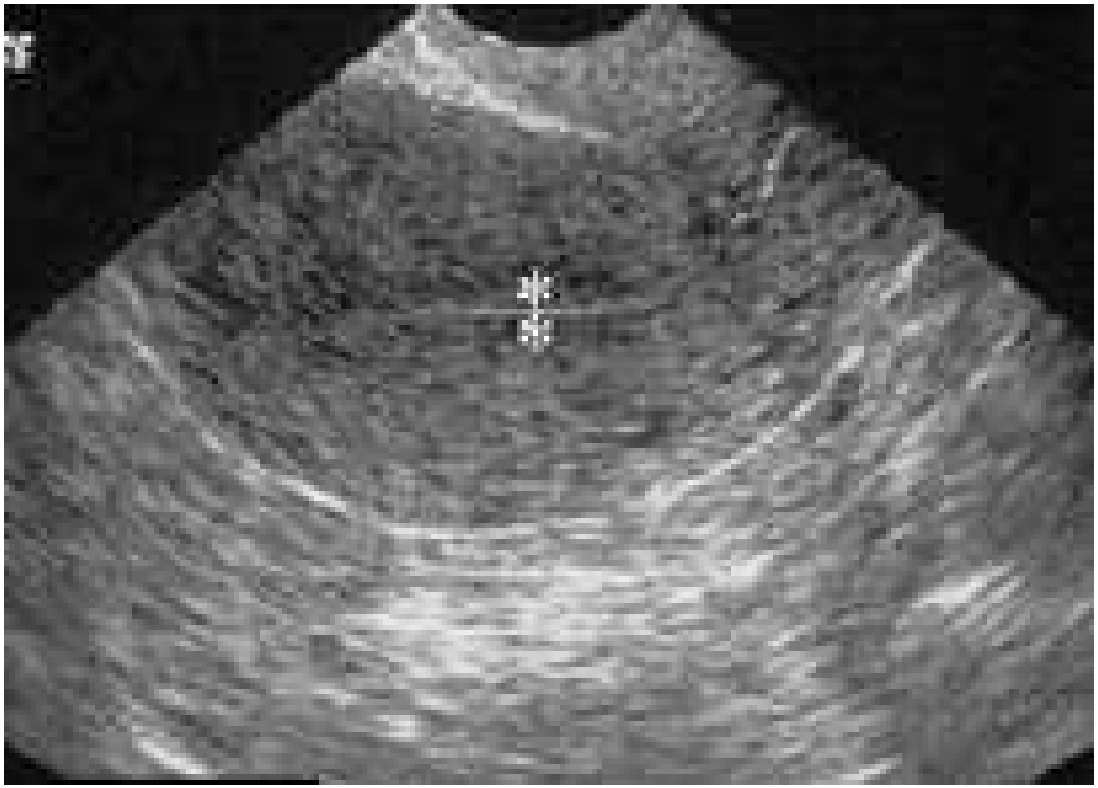
Biochanin A


HO
O
OH
O

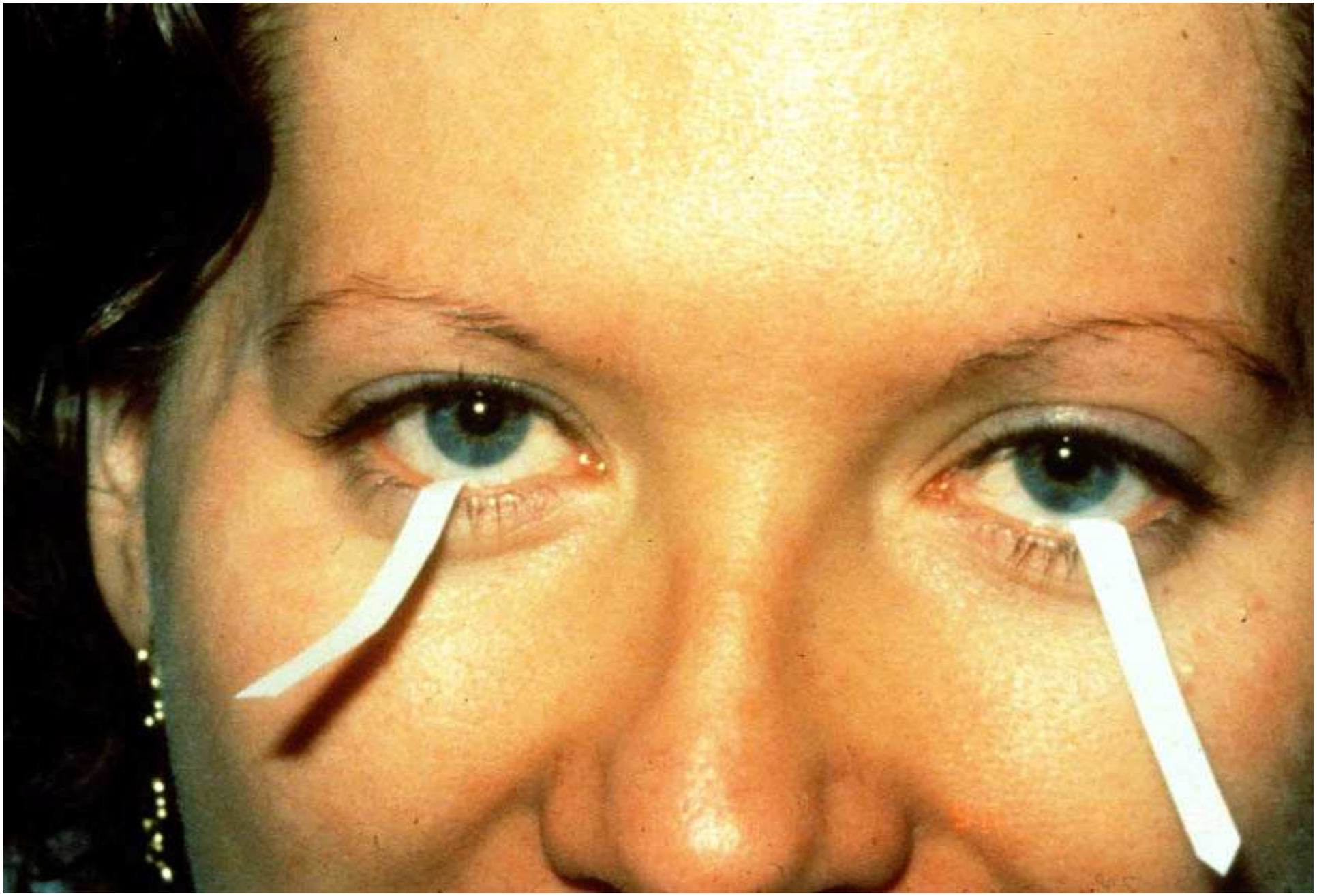
Supra low estrogen replacment therapy

- estradiol-valerat oder benzoat 0.025
- ethanol 96 % 4,0
- propylenglycol ad 10,0 ad

- MDS: estradiol-drops
- 10 drops are 1 mg estradiol
- Event.Sacch.Natrium 0.05 g



Topische Hormontherapie



British Journal of Obstetrics and Gynaecology
January 1998, Vol. 105, pp. 100–102

Treatment of menopausal keratoconjunctivitis sicca with topical oestradiol

***Michael O. Sator** *Registrar*, ***Elmar A. Joura** *Consultant/Lecturer*, ***Thomas Golaszewski** *Consultant*, ***Doris Gruber** *Registrar*, ***Peter Frigo** *Consultant*, ***Markus Metka** *Consultant*, **†Anton Hommer** *Consultant*, ***Johannes C. Huber** *Professor*

**Department of Obstetrics and Gynaecology, Division of Endocrinology and Sterility Treatment, and †Department of Ophthalmology, University of Vienna, Austria*

Objective To investigate the effect of 17β-oestradiol ophthalmic drops in comparison with a traditional tear substitute in postmenopausal women with keratoconjunctivitis sicca.

THE LANCET

Hormonal influences on intraocular pressure

Michael O Sator Doris M Gruber Elmar A Joura

Reprinted from THE LANCET Saturday 14 September 1996
Vol. 348 No. 9029 Pages 761–762


ATHROPATHIA
CLIMACTERICA

Geburtsh. u. Frauenheilk. 48 (1988) 232–234

Der Gelenksschmerz in der Prä- und Postmenopause Arthropathia climacterica

M. Metka , G. Heytmanek , H. Enzelsberger, B. Schurz, Ch. Kurz

I. Univ.-Frauenklinik Wien (Vorstand: Prof. Dr. E. Gitsch)

原　著

DMW 日本語版14(1992), 266－269

高ゴナドトロピン性性腺機能低下性無月経の若年女性におけるホルモン療法前後の骨密度

G. Holzer, M. Metka, G. Heytmanek, W. Knogler und J. Huber
Universitäts-Frauenklinik, Wien

Solving an age-old problem

Western governments need to rethink their approach to dealing with an ageing population.

THERAPEUTICS DOI 10.1111/j.1365-2133.2005.06685.x

Effects and side-effects of 2% progesterone cream on the skin of peri- and postmenopausal women: results from a double-blind, vehicle-controlled, randomized study

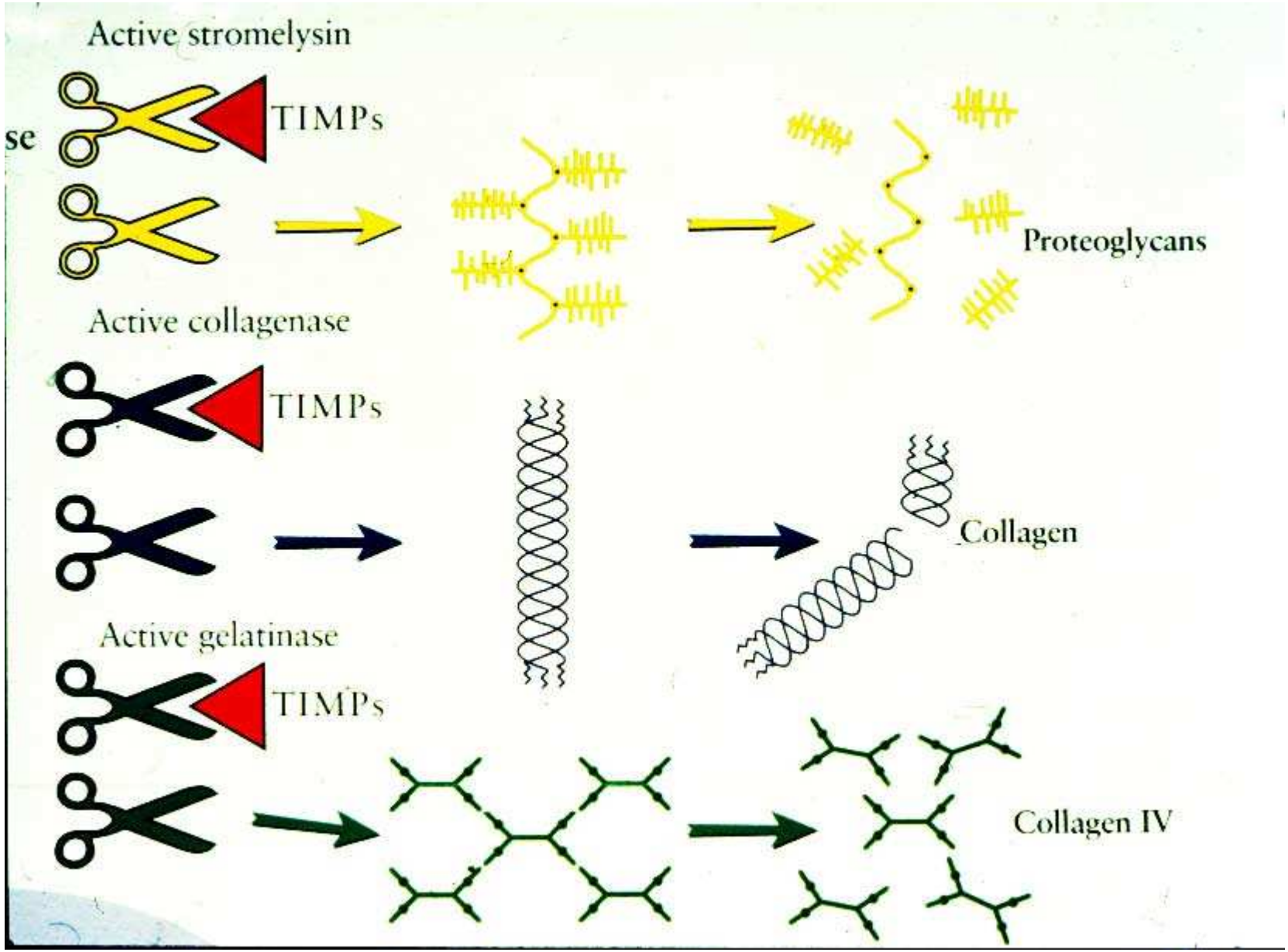
G. Holzer, E. Riegler, H. Hönigsmann, S. Farokhnia* and B. Schmidt

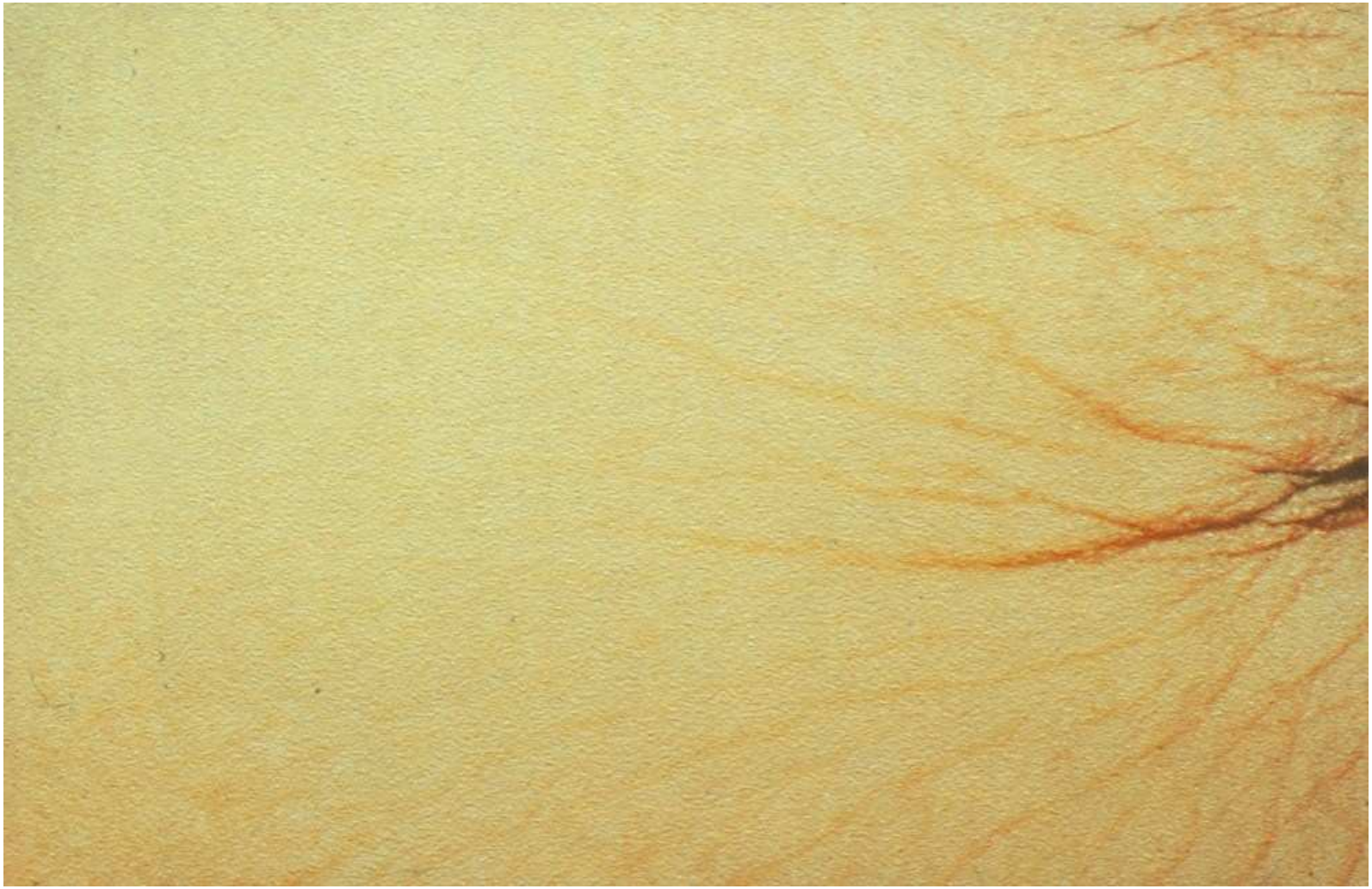
Division of Special and Environmental Dermatology, Medical University of Vienna, Währinger Gürtel 18–20, A-1090 Vienna, Austria
**Pharmacy Department, General Hospital of Vienna, Währinger Gürtel 18–20, A-1090 Vienna, Austria*

Correspondence
Dr Gregor Holzer.
E-mail: gregor.holzer@meduniwien.ac.at

Summary

Background For many years topical progesterone has been prescribed by gynaecologists as an antiageing and skin-firming treatment, without any clinical scientific evidence of its effects, tolerability and safety when applied to skin.

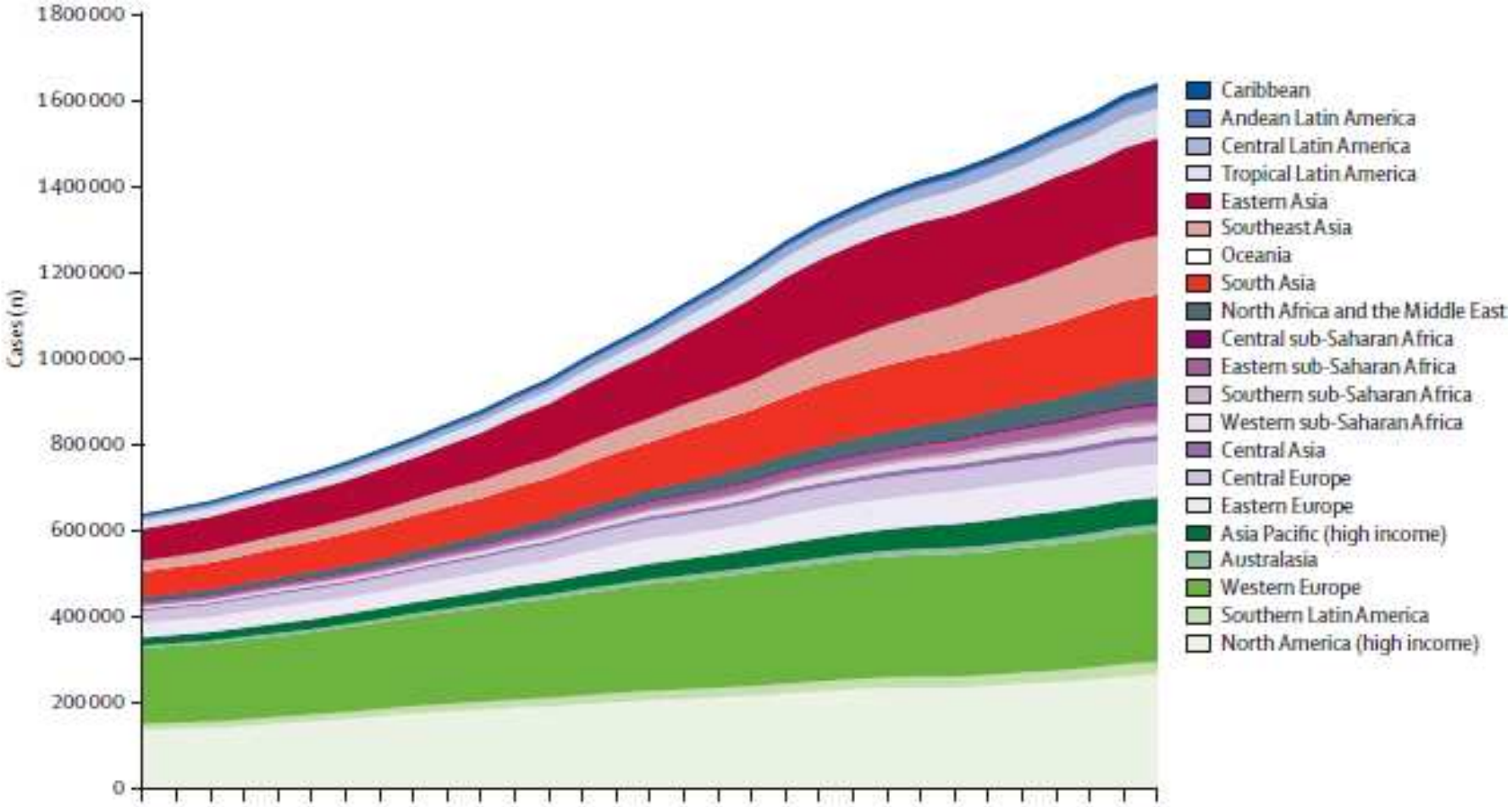

Active stromelysin
se
TIMPs
Proteoglycans
Active collagenase
TIMPs
Collagen
Active gelatinase
TIMPs
Collagen IV



Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis

Mohammad H Forouzanfar, Kyle J Foreman, Allyne M Delossantos, Rafael Lozano, Alan D Lopez, Christopher J L Murray, Mohsen Naghavi

www.thelancet.com Published online September 15, 2011 DOI:10.1016/S0140-6736(11)61351-2



www.thelancet.com Published online September 15, 2011 DOI:10.1016/S0140-6736(11)61351-2

Der große Prostata-Irrtum

Denn in Zahlen ausgedrückt würde eine 20%ige Mortalitätssenkung im Sinne der ERSPC-Studie bedeuten, dass sich 1410 Männer dem Screening unterziehen, davon 48 operiert werden bzw. im Sinne der „active Surveillance" zumindest biopsiert werden, damit letztendlich 1 Patient vor dem Tod bewahrt werden kann [3]. Zweifelsohne gilt es jeden Tod durch ein Karzinom zu verhindern, der Preis den 47 weitere Männer mit oben genannten psychischen und physischen Belastungen dafür bezahlen, ist jedenfalls erheblich.