CHEMICAL TOXICITY AND BREAST HEALTH: A METABOLIC PERSPECTIVE MINUS THE FEAR

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April 3, 2011


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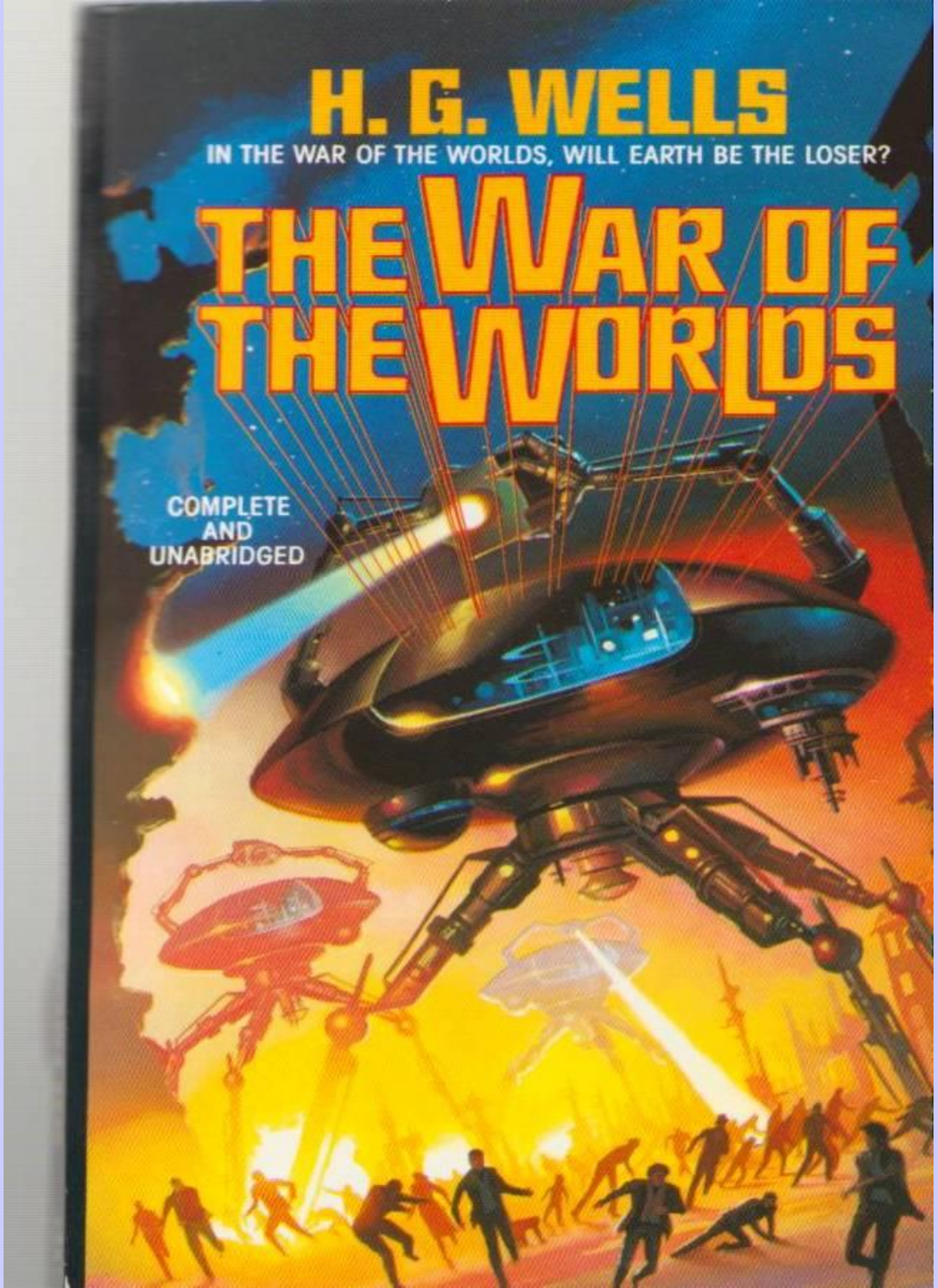
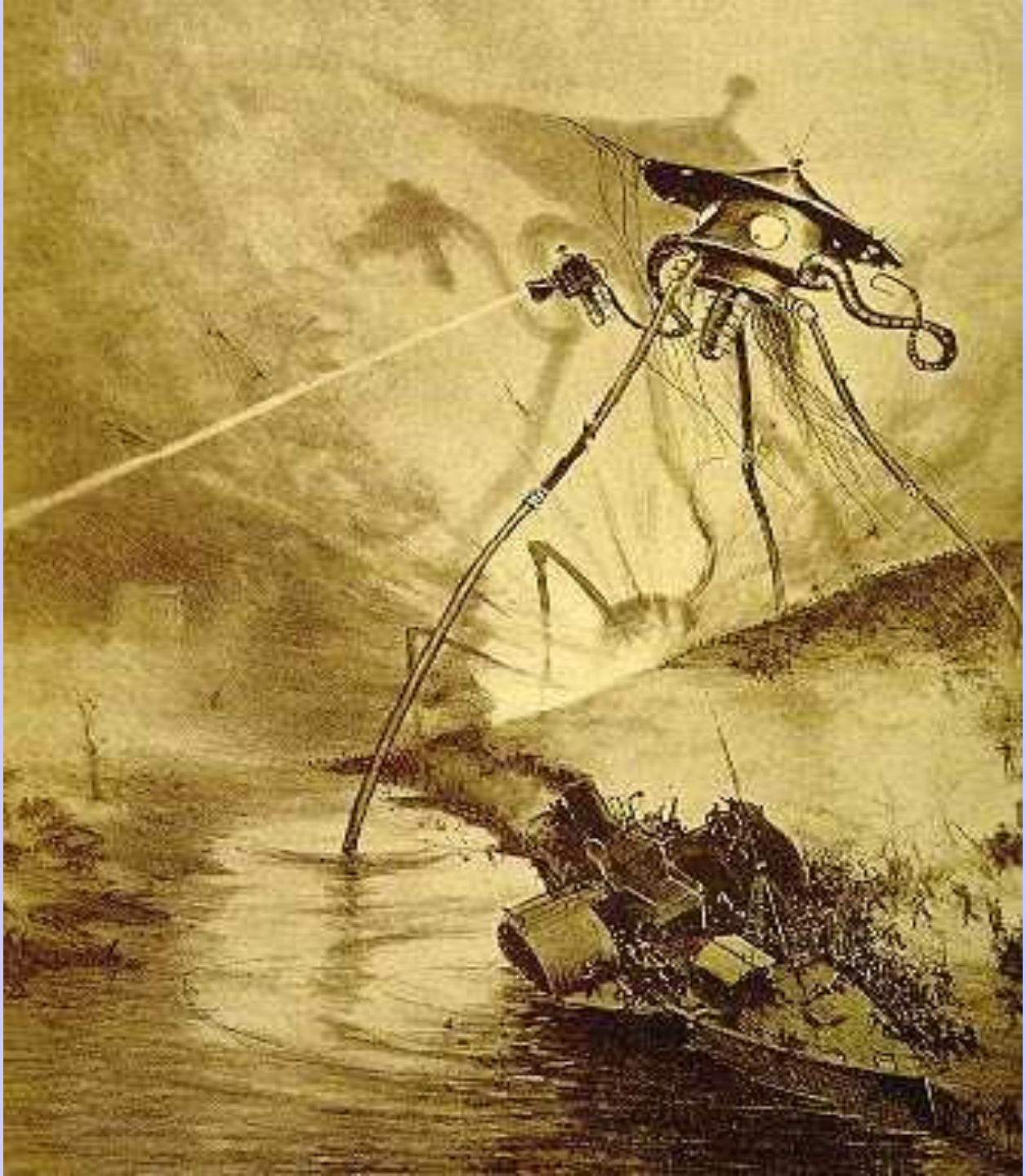

H. G. WELLS
IN THE WAR OF THE WORLDS, WILL EARTH BE THE LOSER?
THE WAR OF THE WORLDS
COMPLETE AND UNABRIDGED

- “…the Martians –*dead!* – slain by the putrefactive and disease bacteria against which their systems were unprepared; slain as the red weed was being slain; slain, after all man’s devices had failed, by the humblest things that God, in his wisdom, has put upon this earth.”
- “These germs of disease have taken toll of humanity since the beginning of things—taken toll of our prehuman ancestors since life began here. But by virtue of this natural selection of our kind we have developed resisting power; to no germs do we succumb without a struggle, and to many—those that cause putrefaction in dead matter, for instance—our frames are altogether immune.”

- “That they did not bury any of their dead, and the reckless slaughter they perpetrated, point also to an entire ignorance of the putrefactive process.”
- “For so it had come about, as indeed I and many men might have forseen had not terror and disaster blinded our minds.”



Obligatory, fear based introduction to mercury

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Study: Even "BPA-Free" Plastics Leach Endrocrine-Disrupting Chemicals

By **BRYAN WALSH** Tuesday, March 8, 2011

Plastics. They seem so...inert. Slow to erode or decay, with a biodegradation time measured in the hundreds of years, plastics appear cut off from the organic environment in the way that no other product is, safe and secure and sterile. Yet scientists have begun to learn that plastics are anything but impermeable.

Plastic containers and linings — especially those used in food containers that might end up being heated or washed — often leach chemicals into the surrounding environment. And some of those chemicals like bisphenol-A (BPA) and phthalates may do strange things to the body, mimicking and disrupting hormones in ways that haven't yet been fully understood.

While the science over such "endocrine-disrupting" chemicals is still far from certain, enough researchers have raised worries that some parents have begun avoiding some plastics in an effort to shield children from toxins. (Pregnant women and infant children seem especially vulnerable to endocrine-disrupting chemicals.) Manufacturers have even begun advertising some products as "BPA-free."

(**More on Time.com:** Pregnant Women Awash in Chemicals. Is That Bad for Baby?)

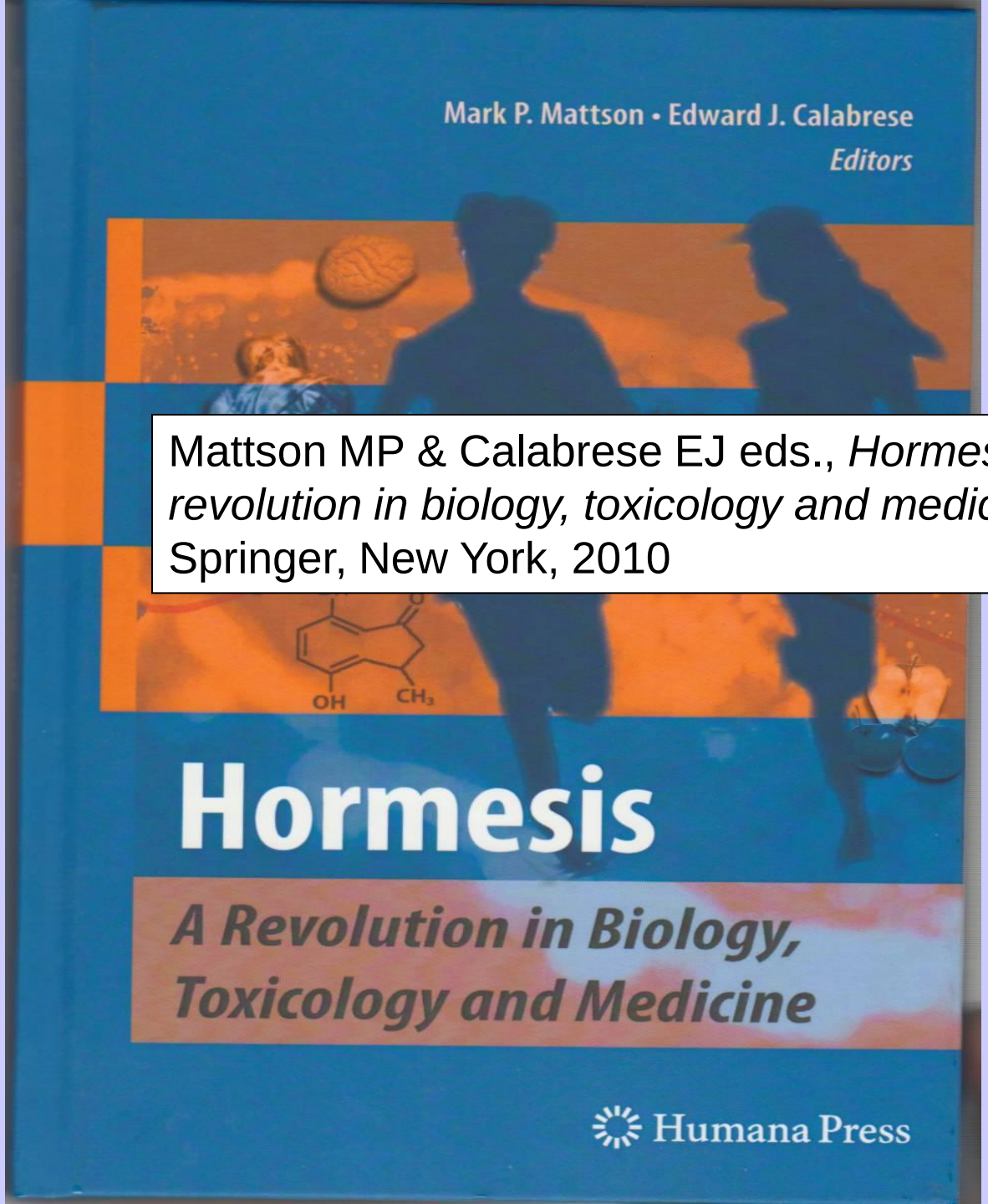
Beijing might have the right idea, because it may turn out that endocrine-disrupting chemicals like BPA are even more common than we imagined. In a new study for the journal *Environmental Health Perspectives*, researchers found that most plastic products leach endocrine-disrupting chemicals — and that was true even for products labeled "BPA-free." Scientists led by George Bittner, a neurobiologist at the University of Texas, looked at 455 common plastic products and found that 70% tested positive for estrogenic activity. Once those products were subject to real-world conditions — microwaving or dishwashing — that proportion rose to 95%. As the study concluded:

> Almost all commercially available plastic products we sampled, independent of the type of resin, product, or retail source, leached chemicals having reliably-detectable EA, including those advertised as BPA-free. In some cases, BPA-free products released chemicals having more EA [endocrine activity] than BPA-containing products.

BPA is particularly worrisome simply because it is so common. Nearly every American has some amount of BPA in his or her body, in part because plastics are so ubiquitous. (And the U.S. seems to be especially contaminated — a recent study found that Americans have twice as much BPA in their bodies as Canadians.) The Food and Drug Administration expressed "some concerns" last year about the potential impact of BPA on the brains of fetuses, infants and children — but no federal agency has yet said that BPA or any other potentially endocrine-disrupting chemicals are unsafe.

(**More on Time.com:** Study: BPA Exposure May Reduce Chances of IVF)

Washington may be reluctant to act, but other authorities are moving forward. Cities and states including Connecticut and Minnesota are working to restrict BPA in baby products, while even China — not exactly a country on the forefront of environmental protection — is reportedly planning to ban BPA in children's products. Even some corporations are

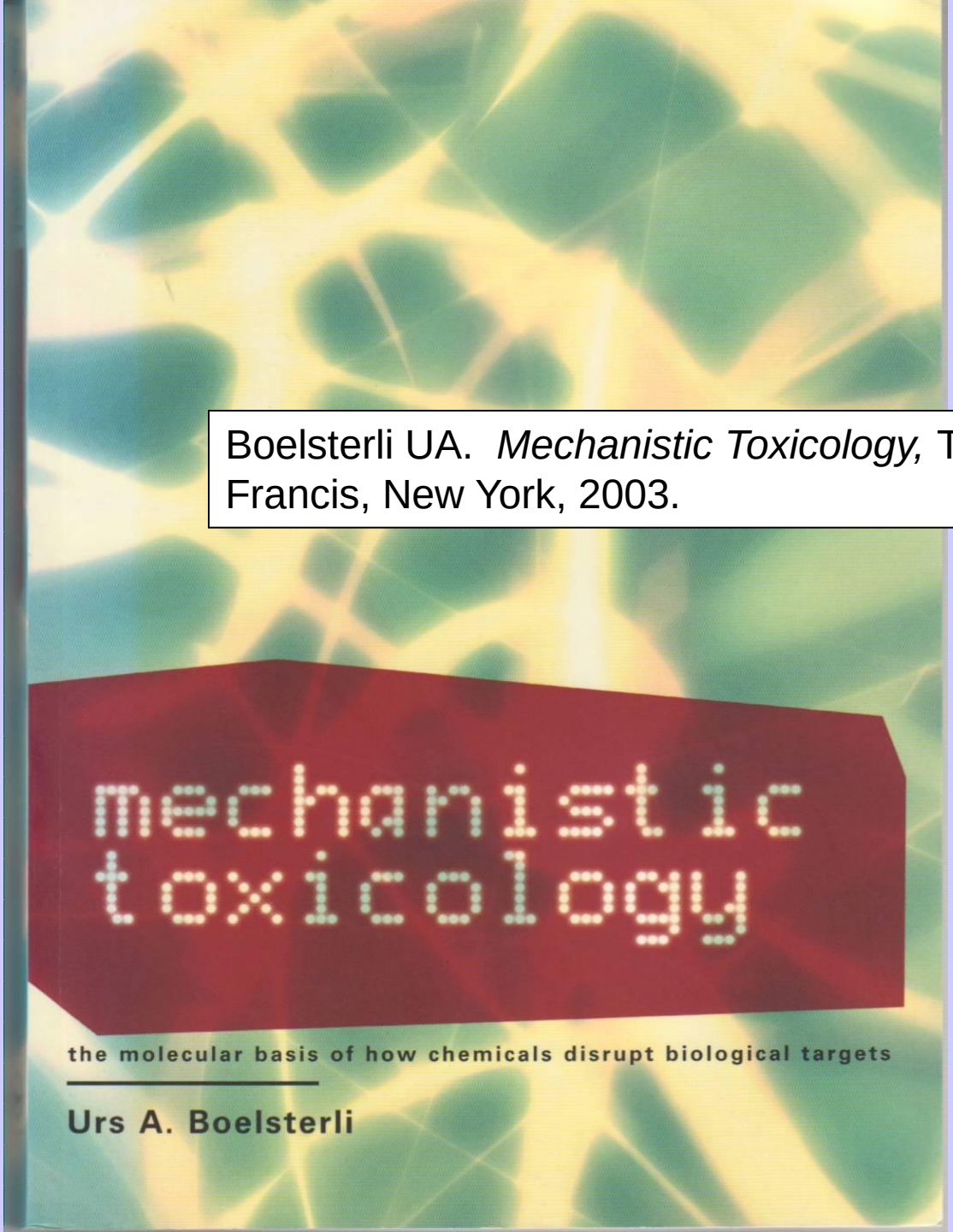


Mattson MP & Calabrese EJ eds., *Hormesis: A revolution in biology, toxicology and medicine*, Springer, New York, 2010

- “The term *hormesis* is defined as ‘a process in which exposure to a low dose of a chemical agent or environmental factor that is damaging at higher doses induces an adaptive effect on the cell or organism.’’

"All things are poison and nothing is without poison, only the dose permits something not to be poisonous" -Paracelsus

Detoxification Basics



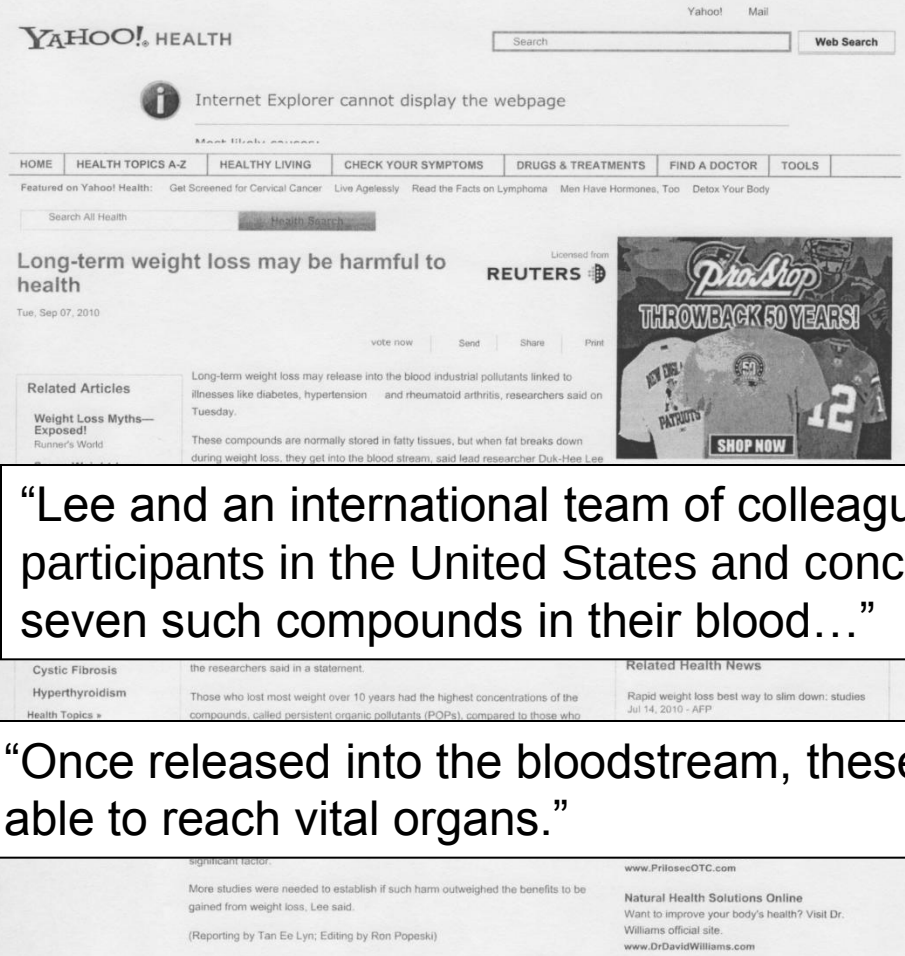
Boelsterli UA. *Mechanistic Toxicology,* Taylor & Francis, New York, 2003.

- “After a xenobiotic has entered the body, higher organisms have the capacity to get rid of the compound (unless it is used for the organism’s intermediate metabolism), thus avoiding accumulation.”
- “If the xenobiotic is hydrophilic, it can readily be excreted in the urine. However, the more hydrophilic a xenobiotic is, the more difficult it becomes to excrete it via the kidneys.”

- “The body has basically two ways of handling such lipophilic compounds. The first option is to store it in the body’s lipophilic compartments.”
- “This happens with many extremely lipophilic compounds, e.g., polychlorinated xenobiotics, which are difficult to metabolize.”
- “Normally, such a sequestered compound poses no harm and can remain in these lipophilic compartments for many months or years.”

“It is only upon rapid release of the body’s fat stores that the compound may suddenly reach high systemic concentrations.”

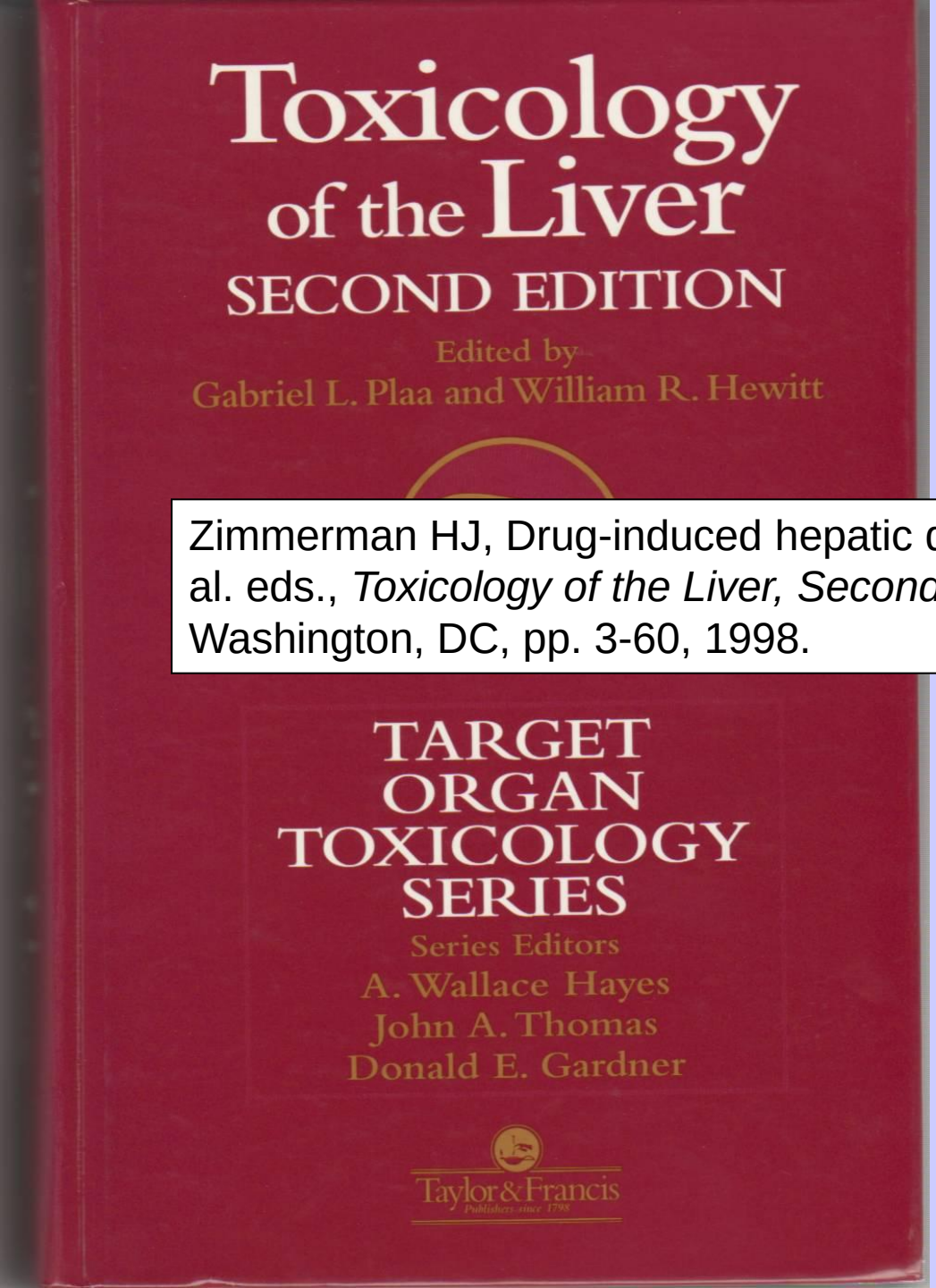
“The second option is to enzymatically convert the lipophilic compound to a more hydrophilic species.”



"Lee and an international team of colleagues studied 1,099 participants in the United States and concentrations of seven such compounds in their blood…"

"Once released into the bloodstream, these pollutants are able to reach vital organs."

"Those who lost most weight over 10 years had the highest concentrations of the compounds, called persistent organic pollutants (POPs), compared to those who gained or maintained a steady weight."



Zimmerman HJ, Drug-induced hepatic disease, in Hayes AW et al. eds., *Toxicology of the Liver, Second Edition,* Taylor & Franis, Washington, DC, pp. 3-60, 1998.

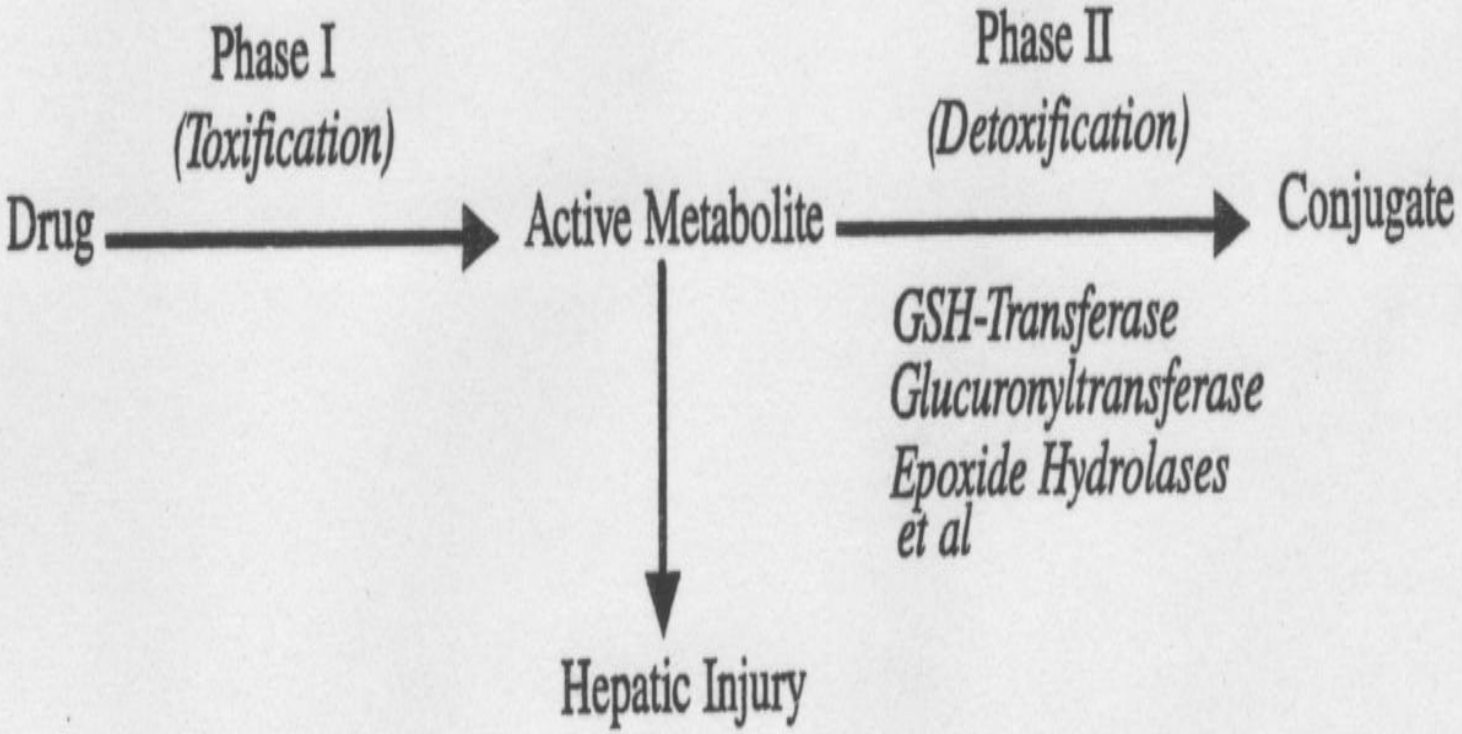
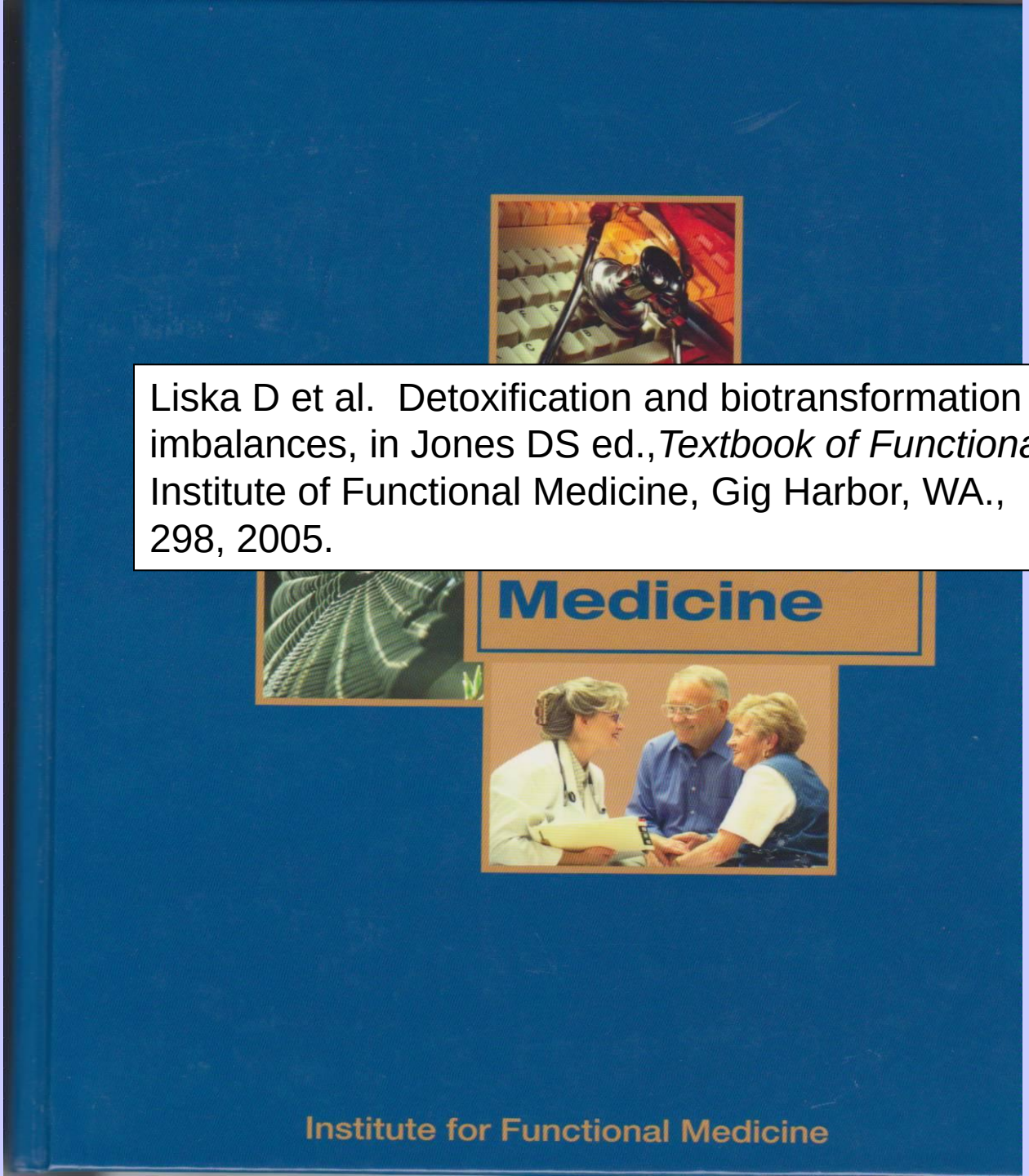
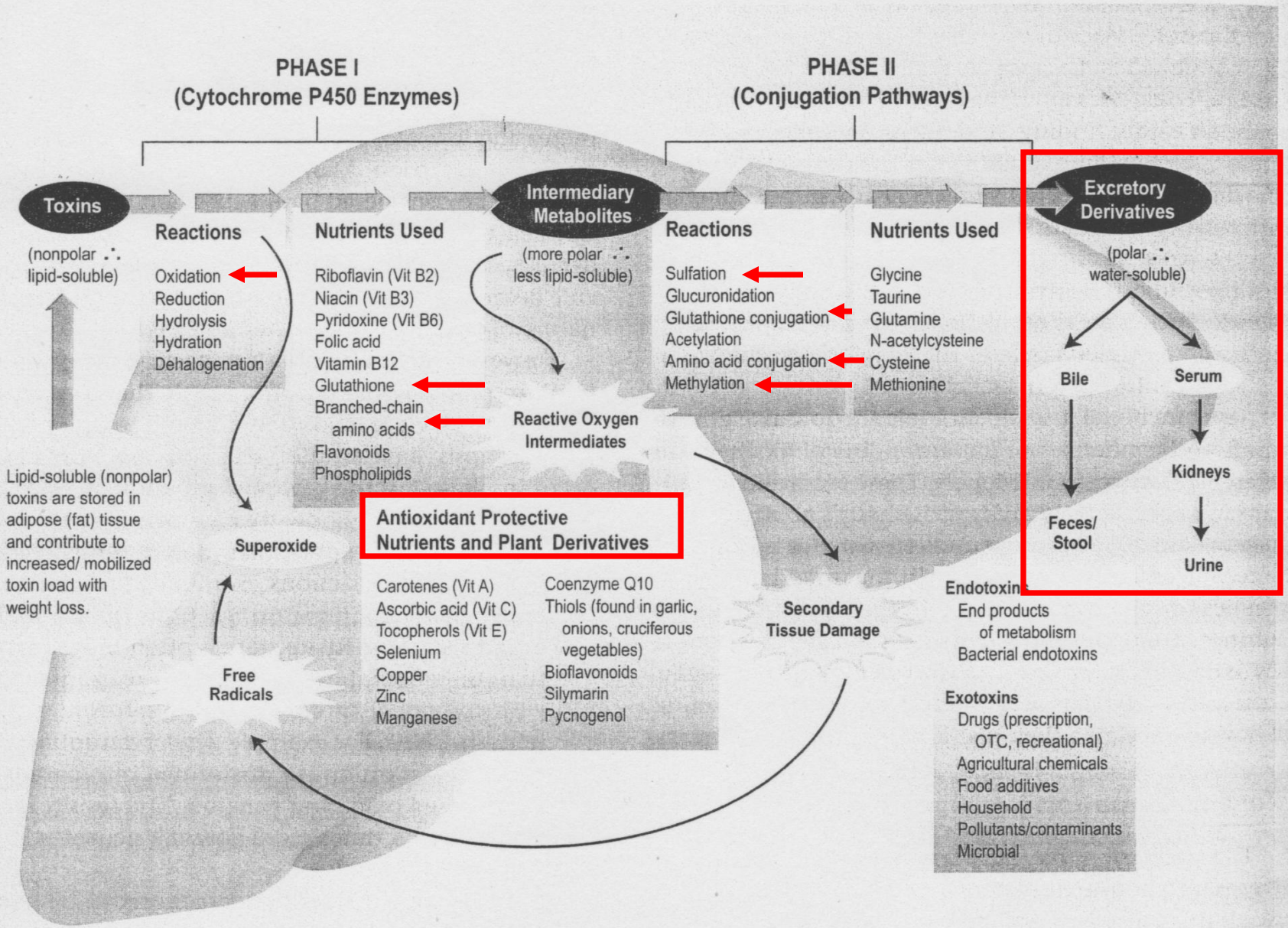


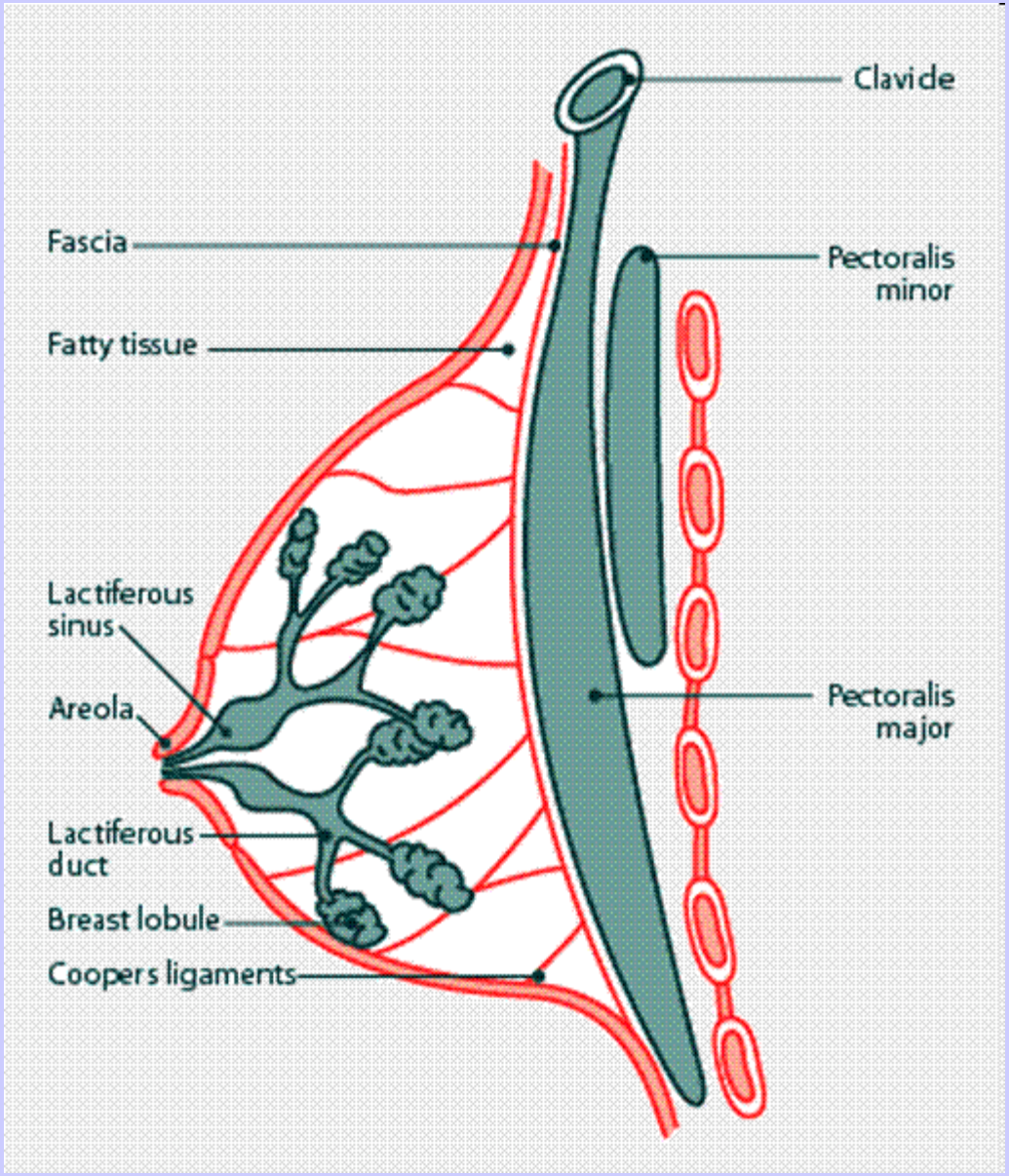
FIG. 2. Schematic representation of drug metabolism. Phase I is catalyed by cytochrome P450, Phase II by one of the enzymes that converts the active intermediate to a nontoxic excretable product. The active metabolite can produce hepatic injury.



Liska D et al. Detoxification and biotransformation imbalances, in Jones DS ed.,*Textbook of Functional Medicine,* Institute of Functional Medicine, Gig Harbor, WA., pp. 275-298, 2005.


PHASE I
(Cytochrome P450 Enzymes)
PHASE II
(Conjugation Pathways)
Toxins
(nonpolar ∴ lipid-soluble)
Reactions
Oxidation
Reduction
Hydrolysis
Hydration
Dehalogenation
Nutrients Used
Riboflavin (Vit B2)
Niacin (Vit B3)
Pyridoxine (Vit B6)
Folic acid
Vitamin B12
Glutathione
Branched-chain amino acids
Flavonoids
Phospholipids
Intermediary Metabolites
(more polar ∴ less lipid-soluble)
Reactions
Sulfation
Glucuronidation
Glutathione conjugation
Acetylation
Amino acid conjugation
Methylation
Nutrients Used
Glycine
Taurine
Glutamine
N-acetylcysteine
Cysteine
Methionine
Excretory Derivatives
(polar ∴ water-soluble)
Bile
Serum
Kidneys
Feces/ Stool
Urine
Lipid-soluble (nonpolar) toxins are stored in adipose (fat) tissue and contribute to increased/ mobilized toxin load with weight loss.
Reactive Oxygen Intermediates
Superoxide
Free Radicals
Antioxidant Protective Nutrients and Plant Derivatives
Carotenes (Vit A)
Ascorbic acid (Vit C)
Tocopherols (Vit E)
Selenium
Copper
Zinc
Manganese
Coenzyme Q10
Thiols (found in garlic, onions, cruciferous vegetables)
Bioflavonoids
Silymarin
Pycnogenol
Secondary Tissue Damage
Endotoxin
End products of metabolism
Bacterial endotoxins
Exotoxins
Drugs (prescription, OTC, recreational)
Agricultural chemicals
Food additives
Household
Pollutants/contaminants
Microbial

Why the breast?


Clavicle
Fascia
Pectoralis minor
Fatty tissue
Lactiferous sinus
Areola
Pectoralis major
Lactiferous duct
Breast lobule
Coopers ligaments

Genetics or environment?

European Journal of Human Genetics (2009) 17, 722–731

www.nature.com/ejhg

REVIEW

Breast cancer susceptibility: current knowledge and implications for genetic counselling

Tim Ripperger[1], Dorothea Gadzicki[1], Alfons Meindl[2] and Brigitte Schlegelberger*[,1]

[1]*Institute of Cell and Molecular Pathology, Hannover Medical School, Hannover, Germany;* [2]*Department of Obstetrics and Gynaecology, Technical University, Munich, Germany*

Breast cancer is the most common malignancy in women in the Western world. Except for the high breast cancer risk in *BRCA1* and *BRCA2* mutation carriers as well as the risk for breast cancer in certain rare

mutation carriers. This review not only outlines the recent key developments and potential clinical benefit for preventive management and therapy but also discusses the current limitations of genetic testing of variants associated with intermediate and low breast cancer risk.

European Journal of Human Genetics (2009) **17**, 722–731; doi:10.1038/ejhg.2008.212; published online 17 December 2008

Keywords: hereditary breast and ovarian cancer; breast cancer susceptibility; low penetrance genes; modifier genes; genetic counselling; single nucleotide polymorphisms (SNPs)

Ripperger T et al. Breast cancer susceptibility: current knowledge and implications for genetic counseling, *Eur J Human Genetics*, Vol. 17, pp. 722-731, 2009

Introduction

With an average lifetime risk of 8–10%, breast cancer is the most common malignancy in women in the Western world. Up to 15% of healthy women have at least one first-degree relative with breast cancer[1] and empirical data show that breast cancer risk doubles in these women. It is assumed that monogenic traits account for 5% of breast cancer overall.[2] Germline *BRCA1* or *BRCA2* mutations, which account for 20–40% of breast cancer that clusters in families and less than 5% of breast cancer overall,[3] are associated with a high lifetime risk of up to 60–85% for breast cancer as well as an increased risk for ovarian cancer. In addition to this high risk in hereditary breast and ovarian cancer, there are certain heritable syndromes associated with an increased breast cancer risk. However, more than 50% of the genetic predisposition to familial breast cancer remains unexplained.[4–6]

In this review, an overview of the most recently published breast cancer susceptibility genes and single nucleotide polymorphisms (SNPs) is given. Besides these current findings, many other SNPs linked to breast cancer susceptibility were found in the past, but the objective of this paper is to review the recent findings in breast cancer genetic susceptibility identified in candidate gene approaches of genes involved in DNA repair and huge

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Received 9 January 2008; revised 22 September 2008; accepted 1 October 2008; published online 17 December 2008

- “With an average lifetime risk of 8-10%, breast cancer is the most common malignancy in women in the Western world.”
- “Up to 15% of healthy women have a least one first degree relative with breast cancer and empirical data show that breast cancer risk doubles in these women.”
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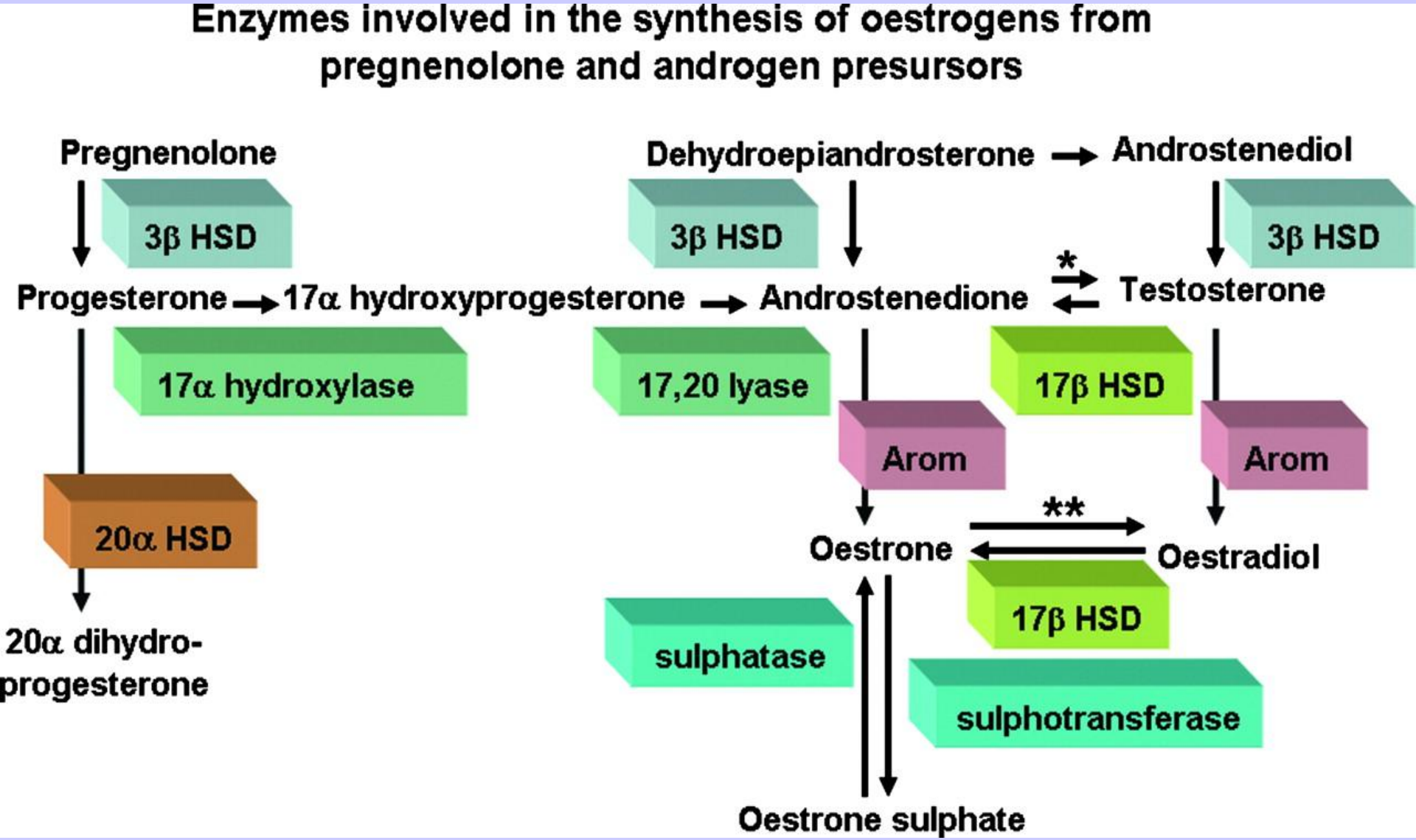
- “Germline BRCA1 or BRCA2 mutations, which acccount for 20-40% of breast cancer that clusters in families and less than 5% of breast cancer overall, are associated with a high lifetime risk of up to 60-85% for breast cancer as well as an increased risk for ovarian cancer.”

Basics of estrogen metabolism

Three primary forms of estrogen

- Estradiol – E2
- Estriol – E3
- Estrone – E1



Rice S & Whitehead SA. Phytoestrogens and breast cancer – promoters or protectors? *Endocrine-Related Cancer,* Vol. 13, pp. 995-1015, 2006.

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Detoxification basics of estrogen

- "The clearance of estrogen from the circulation begins in the liver."
- "Estrogen is excreted from the body by hepatic conjugation to glucuronides and sulfates."
- "Nearly 80% of these products are then excreted in the urine, and the remaining 20% in the bile."
- ***"Any process that interferes with the clearance of estrogen could result in elevated levels of circulating estrogen."***

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The Journal of Steroid Biochemistry & Molecular Biology
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Influences on circulating oestrogens in postmenopausal women: Relationship with breast cancer

Anne Kendall, Elizabeth J. Folkerd, Mitch Dowsett*

Academic Department of Biochemistry, The Royal Marsden NHS Foundation Trust, Fulham Road, London SW3 6JJ, United Kingdom

Received 10 March 2006; accepted 31 July 2006

Abstract

Sex hormones are intrinsically linked to the devel
with elevated breast cancer risk in the postmenop
groups. This review aims to evaluate the impact of
physiological sex hormone profiles. The role of ge
future epidemiological studies and breast cancer ri

Keywords: Oestrogen; Postmenopausal; Breast cancer

Kendall A et al. Influences on circulating oestrogens in postmenopausal women: relationship with breast cancer, *J Steroid Biochem Mol Biol*, Vol. 103, No. 2, pp. 99-109, February 2007

1. Introduction

With the average age at death in the de
rising, there is an increasingly large popu
menopausal women. A significant number of
and die with diseases that are influenced by
nous sex hormone milieu. Breast cancer whic
13,000 deaths per annum in the United Ki
been known to be affected by ovarian functi
when Sir George Beatson observed that some cancers in pre-menopausal women regressed after oophorectomy [2]. Much work has focused on the relationship of oestrogen to breast cancer incidence. It is possible that those at increased risk of developing breast cancer by virtue of high oestradiol levels might benefit from endocrine chemoprevention.

However to incorporate oestradiol levels into risk algorithms for breast cancer, a clear picture is needed of which factors influence (i) normal physiological oestrogen levels in this group and (ii) the measurement of such levels. The main aim of this review is to consider such factors and their relative importance in the context of future epidemiological studies and the development of risk algorithms in relation to breast

Several groups have now published prospective data on endogenous hormones and breast cancer but none have individually been large enough to give accurate estimates of risk. The Endogenous Hormones and Breast Cancer Collaborative Group [3] was set up to analyse the original pooled data from nine such trials. The adjusted relative risk of breast cancer for women whose oestradiol levels were in the top quintile compared with those in the bottom quintile was 2.00 (95% CI: 1.47–2.71). The overall estimate of RR of breast cancer associated with the doubling of oestradiol was 1.29 (95% CI: 1.15–1.44, $P < 0.001$). There was wide heterogeneity in hormone levels due to different assays in different laboratories but there was no statistically significant heterogeneity between studies for the association of any of the hormones with breast cancer risk. There was no evidence that blood collected within 2 years of diagnosis showed higher relative

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doi:10.1016/j.jsbmb.2006.07.011

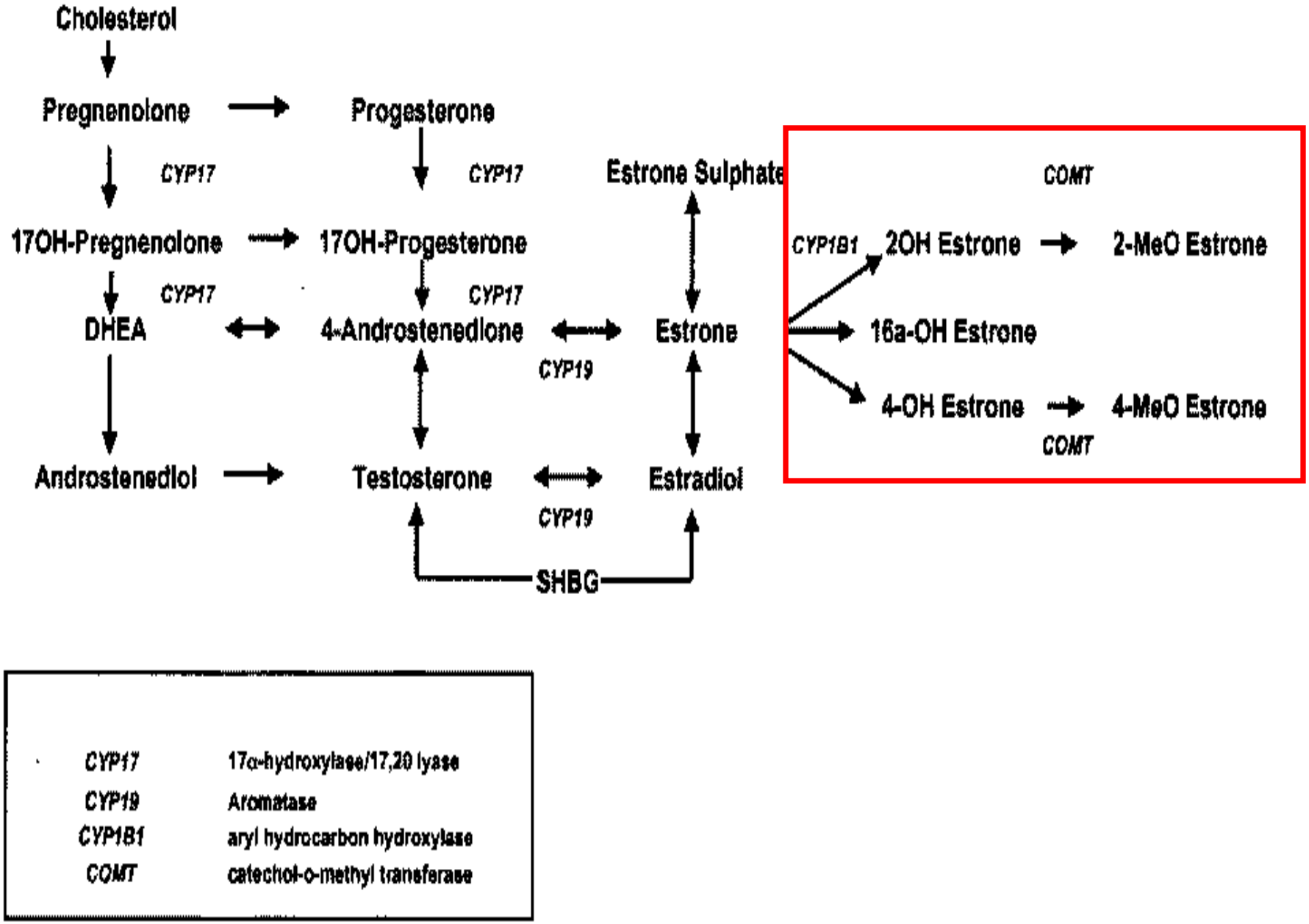

Fig. 1. Principle conversions involved in estrogen synthesis and metabolism.

ONCOLOGY REPORTS 14: 1091-1096, 2005

Relative imbalances in the expression of estrogen-metabolizing enzymes in the breast tissue of women with breast carcinoma

SEEMA SINGH[1], DHRUBAJYOTI CHAKRAVARTI[1], JAMES A. EDNEY[2], RONALD R. HOLLINS[2], PERRY J. JOHNSON[2], WILLIAM W. WEST[3], SHEILA M. HIGGINBOTHAM[1], ERCOLE L. CAVALIERI[1] and ELEANOR G. ROGAN[1]

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Nebraska Medical Ce

Abstract. Estrogens are a known risk f
Studies indicate that initiation of breas
metabolism of estrogens to form abn
catechol estrogen-3,4-quinones, whic
DNA to form depurinating adducts and
mutations that lead to cancer. Amo
metabolizing estrogens are two activ
chrome P450 (CYP)19 (aromatase), v
gens to estrogens, and CYP1B1, whi
predominantly to the 4-catechol estr
oxidized to catechol estrogen-3,4-quinc
quinones is prevented by methylati
estrogens by the enzyme, catechol-O-methyltransferase (COMT). In addition, catechol estrogen quinones can be reduced back to catechol estrogens by NADPH quinone oxidoreductase 1 (NQO1) and/or are coupled with gluta-

Singh S et al. Relative imbalances in the expression of estrogen-metabolizing enzymes in the breast tissue of women with breast carcinoma, *Oncology Reports*, Vol. 14, No. 4, pp. 1091-6, October 2005.

reacting with DNA, initiate the series of events leading to breast cancer.

Introduction

(4-6). These adducts generate apurinic sites leading to

"The control breast tissues showed lower expression of the activating enzymes, CYP19 and CYP1B1, and higher expression of the deactivating enzymes, COMT and NQ01, compared to the cases. In the cases, the reverse pattern was observed: greater expression of activating enzymes and lower expression of deactivating enzymes."

Estrogen metabolism and breast cancer

[CANCER RESEARCH 60, 4667–4677, September 1, 2000]

Review

Mammary Expression of Xenobiotic Metabolizing Enzymes and Their Potential Role in Breast Cancer[1]

J. Andrew Williams[2] and David H. Phillips

Institute of Cancer Research, Haddow Laboratories, Sutton, Surrey SM2 5NG, United Kingdom

Abstract

Breast cancer is the major cause of cancer death in women worldwide. High penetrance genes account for only 5% of cases, whereas polymorphic low penetrance genes acting in concert with lifestyle/environmental risk factors are likely to account for a much higher proportion. Genotoxic compounds implicated in human breast carcinogenesis include endogenous compounds, estrogens, and dietary or environmental xenobiotics–heterocyclic amines, aromatic amines, polycyclic aromatic hydrocarbons, and nitropolycyclic aromatic hydrocarbons. Here we review evidence for a role of mammary-expressed enzymes that metabolically activate and/or detoxify potential genotoxic breast carcinogens: cytochrome P-450s, catechol-*O*-methyltransferase, epoxide hydrolase, peroxidases, glutathione *S*-transferases, *N*-acet
catalyzing conjugatio
in the light of eviden
metabolic activation i
milk, and for the pres
cells (from which mo
morphisms in the gen
also considered. The
etiology of breast ca
expression should be
tion of polymorphism

Introduction

Each year breast cancer is diagnosed in 910,000 women worldwide, and 376,000 women die from the disease (1). Most of the cases are in industrialized countries (*e.g.*, 180,000 in North America and 220,000 in Europe). The etiology of most breast cancer is obscure. Known risk factors including higher/increased exposure to estrogen are apparent in less than one-third of breast cancer cases, and the relative risks associated with them are numerically low (generally <3; Refs. 1–3).
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cancer susc
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cases occu
rendering t
There is
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lower rates
descendant
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proaching those of the host country (1), strongly implicating lifestyle factors as the major contributors to the development of the disease. Increased risk may be associated with exposure to genotoxic agents during breast development, because the undifferentiated ductal elements of the breast are more susceptible to the action of genotoxins early in life (7). Willett (3) has suggested that dietary and environmental causes may be responsible for up to 50% of breast cancer cases, although the precise nature of the "lifestyle" factors that are causative is unknown.

The ductal system of the adult human breast consists of 15–25 lactiferous ducts, opening at the nipple. The parenchyma of the ducts are composed of luminal epithelial cells lining the ducts and of

tions in "low penetrance" genes encoding carcinogen-metabolizing enzymes (*i.e.*, mutations that resulted in an increase in the rate of an activating metabolic transformation of a carcinogen/mutagen, or in a decrease in the rate of an inactivating one) would lead to increased rates of breast cancer in older women.

Agents Implicated in Human Breast Carcinogenesis

The observation in the 17th century that nuns had a high incidence

cently, extracts of mammary lipid from women undergoing reduction mammoplasty have been shown to possess genotoxic activity (15, 20). Furthermore, extracts of human breast milk have been shown to be genotoxic (21–23), supporting the notion that functional elements of the mammary gland may be exposed to potential tumor initiators. The

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[1] Supported by grants from the Cancer Research Campaign and the Association for International Cancer Research.
[2] To whom requests for reprints should be addressed, at Institute of Cancer Research, Haddow Laboratories, Cotswold Road, Sutton, Surrey SM2 5NG, United Kingdom.

Williams JA & Phillips DH. Mammary expression of xenobiotic metabolizing enzymes and their potential role in breast cancer, *Cancer Res*, Vol. 60, pp. 4667-4677, September 1, 2000.

"Genotoxic compounds implicated in human breast carcinogenesis include endogenous compounds, estrogens, and dietary or environmental xenobiotics-heterocyclic amines, aromatic amines, polycyclic aromatic hydrocarbons, and nitropolycyclic aromatic hydrocarbons."

- “Here we review evidence for a role of mammary-expressed enzymes that metabolically activate and/or detoxify potential genotoxic breast carcinogens: cytochrome P450s, catechol-O-methyltransferase, epoxide hydrolase, peroxidases, glutathione S-transferases, N-acetyltransferases, and other enzymes catalyzing conjugation reactions.”

Cancer Science
The official journal of the Japanese Cancer Association JCA

Immunolocalization of estrogen-producing and metabolizing enzymes in benign breast disease: Comparison with normal breast and breast carcinoma

Yoshie Sasaki,[1] Yasuhiro Miki,[2] Hisashi Hirakawa,[3] Yoshiaki Onodera,[2] Kiyoshi Takagi,[1] Jun-ichi Akahira,[2] Seijiro Honma,[4] Takanori Ishida,[5] Mika Watanabe,[6] Hironobu Sasano[2] and Takashi Suzuki[1,7]

Departments of [1]Pathology and Histotechnology; [2]Anatomic Pathology, Tohoku University Graduate School of Medicine, Sendai; [3]Department of Surgery, Tohoku Kosai Hospital, Sendai; [4]Research and Development Department, ASKA Pharma Medical Co., Ltd., Kanagawa; [5]Department of Surgical Oncology, Tohoku University Graduate School of Medicine, Sendai; [6]Department of Pathology, Tohoku University Hospital, Sendai, Japan

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It is well known that estrogens play important roles in the cell proliferation of breast carcinoma. Benign breast disease (BBD) contains a wide spectrum of diseases, and some are considered an important risk factor f
ment. However, the sig
largely unknown. The
concentrations of estro
producing/metabolizin
findings with those in
in situ (DCIS). Tissue co
significantly (3.4-fold) h
the same (0.7-fold) as
gen sulfotransferase in
normal breast (n = 28)
DCIS (n = 28). Aromata
tended to be higher (P
17β-hydroxysteroid de
significantly higher in BBD than normal breast in the postmenopausal tissues. Immunoreactivity of estrogen and progesterone receptors was also significantly higher in BBD than normal breast. These results suggest that tissue concentration of estradiol is increased in BBD at a level similar to DCIS, which is considered mainly due to loss of estrogen sulfotransferase expression. Increased local estradiol concentration in BBD due to aberrant expression of estrogen-producing/metabolizing enzymes may

estrogen receptor (ER).[5–10] and women who had used postmenopausal hormonal supplementation were reported to be associated with an increased risk of BBD.[11,12] Treatment with

17βHSD2 (oxidation of estradiol to estrone).[17] Pasquali *et al.*[18] reported that estradiol concentration and STS activity was significantly higher in FA than the corresponding normal human breast tissue, and Ariga *et al.*[8] reported immunolocalization of 17βHSD1 and 17βHSD2 in UDH and ADH. However, other information regarding estrogen concentration or estrogen-producing/metabolizing enzymes is unknown in BBD, and the significance of estrogens remains largely uncharacterized in

estrogen actions. Benign breast disease frequently expressed

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doi: 10.1111/j.1349-7006.2010.01673.x

Sasaki Y et al. Immunolocalization of estrogen-producing and metabolizing enzymes in benign breast disease: Comparison with normal breast and breast carcinoma, *Cancer Sci*, Vol. 101, No. 10, pp. 2286-2292, October 2010

"These results suggest that tissue concentration of estradiol is increased in benign breast disease at a level similar to ductal carcinoma in situ…Increased local estradiol concentration in benign breast disease due to aberrant expression of estrogen-producing/metabolizing enzymes may play important roles in the accumulation of estradiol-mediated growth and/or subsequent development of breast carcinoma."

A Unifying Mechanism in the Initiation of Cancer and Other Diseases by Catechol Quinones

ERCOLE L. CAVALIERI AND ELEANOR G. ROGAN

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ABSTRACT: The first step in cancer initiation is the reaction of chemical carcinogens with DNA to form stable adducts, which remain in DNA unless removed by repair, and depurinating adducts, which detach from DNA following destabilization of the glycosyl bond. Depurinating DNA adducts of polycyclic aromatic hydrocarbons play a major role in the initiation of cancer, as shown by the correlation between depurinating adducts and oncogenic mutations of the H-*ras* oncogene in mouse skin. Following these results, experiments on the me-

quinone of the neurotransmitter dopamine can also react with DNA to form N3Ade and N7Gua adducts. The subsequent mutations could be at the origin of Parkinson's and other neurodegenerative diseases. In summary, the apurinic sites produced in DNA from the loss of these depurinating adducts can be converted into mutations by error-prone repair, which may initiate cancer and other diseases.

KEYWORDS: apurinic sites; cancer initiation; catechol estrogen quinones; depurinating DNA adducts; estrogen mutagenicity

INTRODUCTION

Compelling evidence on estrogen metabolism,[1–7] formation of DNA adducts,[8–13] carcinogenicity,[14–17] mutagenicity,[18–21] and cell transformation[22–24] has led to the

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Ann. N.Y. Acad. Sci. 1028: 247–257 (2004). © 2004 New York Academy of Sciences. doi: 10.1196/annals.1322.029

Cavalieri EL & Rogan EG. A unifying mechanism in the initiation of cancer and other diseases by catechol quinones, *Ann NY Acad Sci*, Vol. 1028, pp. 247-257, 2004.

- “Compelling evidence on estrogen metabolism, formation of DNA adducts, carcinogenicity, mutagenicity, and cell transformation has led to the hypothesis that specific estrogen metabolites, predominately catechol estrogen-3-4-quinones, react with DNA to produce the critical mutations initiating breast, prostate, and other cancers.”
- “Estrone (E_1) or estradiol (E_2) can be metabolically transformed to 4-hydroxyE_1(E_2) [4-OHE_1(E_2)] by cytochrome P450 (CYP) 1B1.”

"Oxidation of these catechol estrogens lead to the corresponding 3,4-quinones [E_1(E_2)-3-4-Q], which can react with DNA to form predominately depurinating adducts."

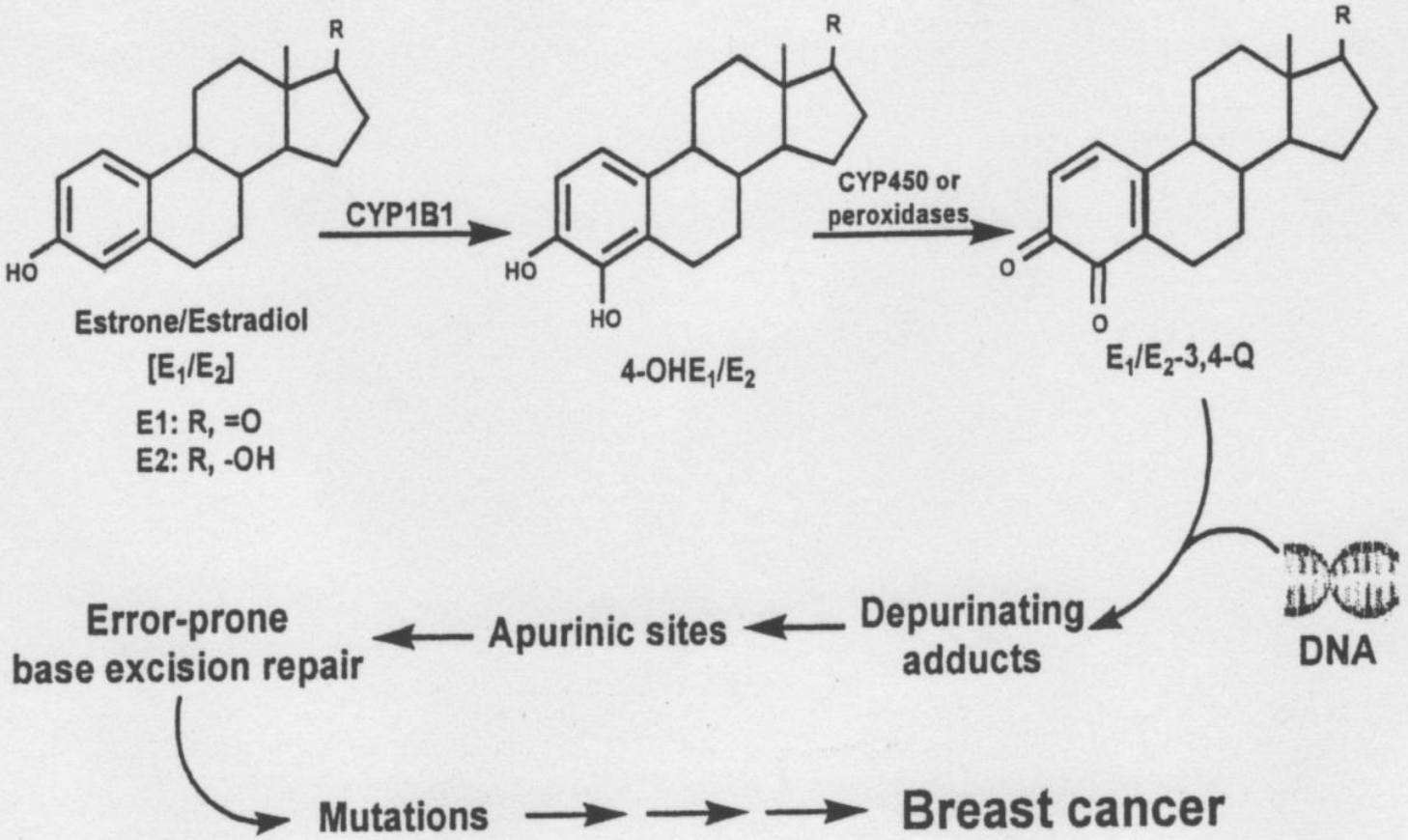

FIGURE 1. Metabolism of $E_1(E_2)$ to 4-$OHE_1(E_2)$ and $E_1(E_2)$-3,4-Q, and reaction of $E_1(E_2)$-3,4-Q with DNA to generate the series of events leading to breast cancer.

- “The estrogen metabolism involves a balance between activating and deactivating (protective) pathways.”
- “This equilibrium is called *estrogen homeostasis* and tends to abrogate or limit the reaction of the endogenous carcinogens $E_1(E_2)$-Q with DNA.”
- “Four major enzymes are involved with estrogen metabolism.”
- “The first is CYP19, aromatase, which regulates the amount of androgen converted to estrogen.”

- “The second activating enzyme is CYP1B1, which catalyzes almost exclusively conversion of estrogens to their corresponding 4-catechol estrogens in extrahepatic tissues.”
- “Important protective pathways are represented by COMT, which methylates catechol estrogens, and quinone reductase, which converts quinones back to catechols.”

- “A third protective pathway is the effective reaction of catechol quinones with glutathione (GSH) such that these quinones do not react with DNA.”
- “Thus, imbalance of estrogen homeostasis is generated by overexpression of activating enzymes and/or inadequate levels of protective enzymes.”

Catechol Quinones of Estrogens in the Initiation of Breast, Prostate, and Other Human Cancers

Keynote Lecture

ERCOLE CAVALIERI AND ELEANOR ROGAN

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ABSTRACT: Estrogens can be converted to electrophilic metabolites, particularly the catechol estrogen-3,4-quinones, estrone(estradiol)-3,4-quinone [$E_1(E_2)$-3,4-Q], which react with DNA to form depurinating adducts. These adducts are released from DNA to generate apurinic sites. Error-prone repair of this damage leads to the mutations

idation of catechols to semiquinones and quinones is a mechanism of tumor initiation not only for endogenous estrogens, but also for synthetic estrogens such as hexestrol and diethylstilbestrol, a human carcinogen. This mechanism is also involved in the initiation of leukemia by benzene, rat olfactory tumors by naphthalene, and neurodegenerative diseases such as Parkinson's disease by dopamine. In fact, dopamine quinone reacts with DNA similarly to the $E_1(E_2)$-3,4-Q, forming analogous depurinating N3Ade and N7Gua adducts. The depurinating adducts that migrate from cells and can be found in body fluids can also serve as biomarkers of cancer risk. In fact, a higher level of estrogen-DNA adducts has been found in the urine of men with prostate cancer and in women with breast cancer compared to healthy controls. This unifying mechanism of the origin of cancer and other diseases suggests preventive

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doi: 10.1196/annals.1386.042**

Cavalieri E & Rogan E. Catechol quinones of estrogens in the initiation of breast, prostate, and other human cancers, *Ann NY Acad Sci*, Vol. 1089, pp. 286-301, 2006.

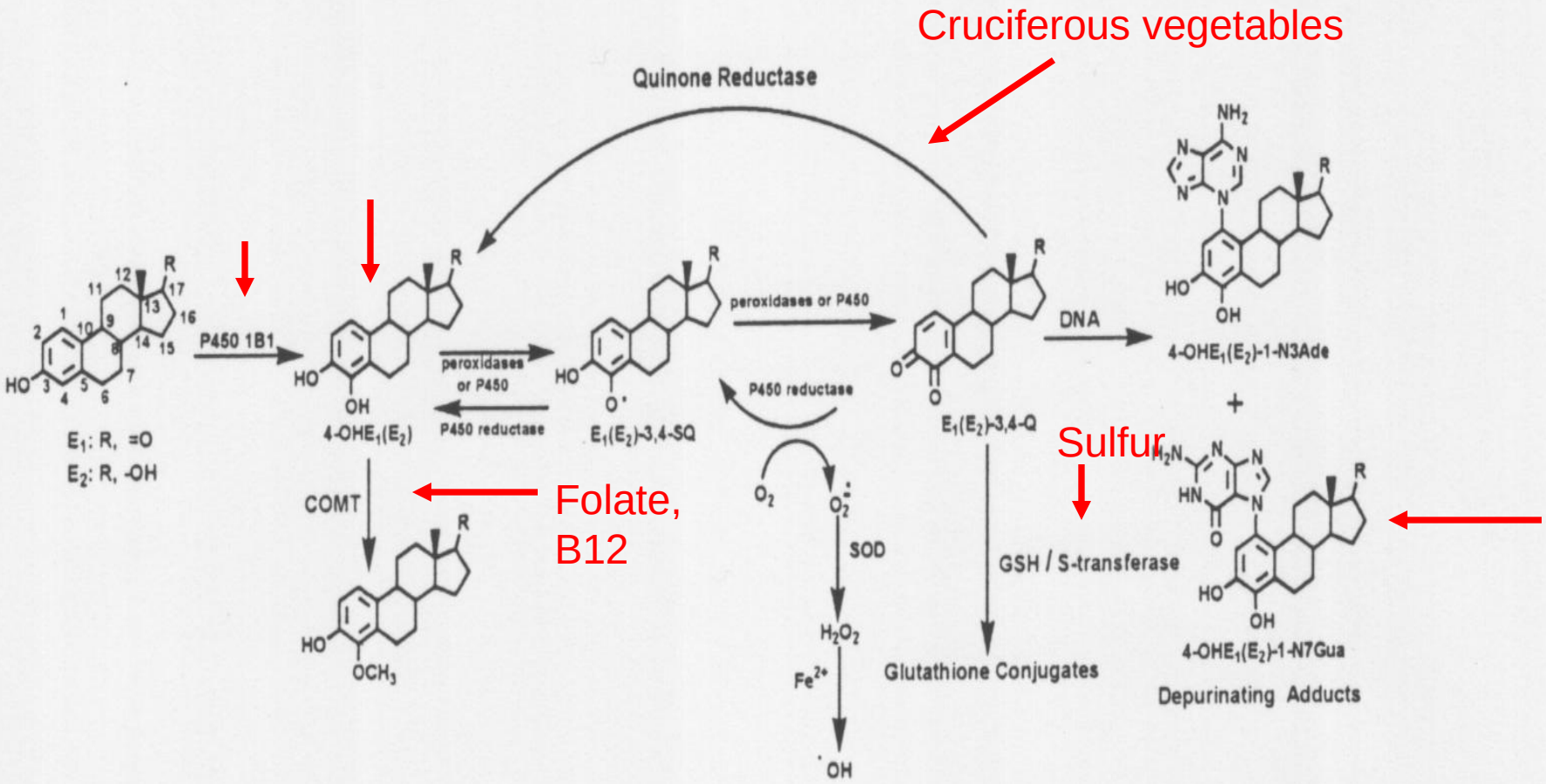

FIGURE 2. Formation, metabolism, and DNA adducts of 4-$OHE_1(E_2)$.

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Review

Catechol estrogen quinones as initiators of breast and other human cancers: Implications for biomarkers of susceptibility and cancer prevention ☆

Ercole Cavalieri [a,*], Dhubajyoti Chakravarti [a], Joseph Guttenplan [b], Elizabeth Hart [c], James Ingle [d], Ryszard Jankowiak [e], Paola Muti [f], Eleanor Rogan [a], Jose Russo [g], Richard Santen [h], Thomas Sutter [i]

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Cavalieri E et al. Catechol estrogen quinones as initiators of breast and other human cancers: Implications for biomarkers of susceptibility and cancer prevention, *Biochimica et Biophysica Acta*, Vol. 1766, pp. 63-78, 2006

Abstr

Exposure to estrogens is associated with increased risk of breast and other types of human cancer. Estrogens are converted to metabolites, particularly the catechol estrogen-3,4-quinones (CE-3,4-Q), that can react with DNA to form depurinating adducts. These adducts are released from DNA to generate apurinic sites. Error-prone base excision repair of this damage may lead to the mutations that can initiate breast, prostate and other types of cancer.

The reaction of CE-3,4-Q with DNA forms the depurinating adducts 4-hydroxyestrone(estradiol) [4-OHE$_1$(E$_2$)-1-N3Ade and 4-OHE$_1$(E$_2$)-1-N7Gua. These two adducts constitute more than 99% of the total DNA adducts formed. Increased levels of these quinones and their reaction with DNA occur when estrogen metabolism is unbalanced. Such an imbalance is the result of overexpression of estrogen activating enzymes and/or deficient expression of the deactivating (protective) enzymes. This unbalanced metabolism has been observed in breast biopsy tissue from women with breast cancer, compared to control women. Recently, the depurinating adduct 4-OHE$_1$(E$_2$)-1-N3Ade has been detected in the urine of prostate cancer patients, but not in urine from healthy men.

"Another critical factor unbalancing estrogen homeostasis may be higher levels of 4-OHE$_1$(E$_2$) due to overexpression of CYP1B1, which converts E$_2$ predominantly to 4-OHE$_2$."

COMT, catechol-*O*-methyltransferase; CYP, cytochrome P450; CYP19, aromatase; E$_1$, estrone; E$_2$, estradiol; E$_2$-3,4-Q, estradiol-3,4-quinone; ER, estrogen receptor; ERKO, estrogen receptor α-knock out; FASS, field amplified sample stacking; GSH, glutathione; H, Harvey; HBEC, human breast epithelial cells; LC/MS/MS, ultraperformance liquid chromatography/tandem mass spectrometry; LOD, limit of detection; LOH, loss of heterozygosity; MAb, monoclonal antibody; OHE$_2$, hydroxyestradiol; 4-OHE$_1$(E$_2$)-1-N3Ade, 4-hydroxyestrone(estradiol)-1-N3Adenine; 4-OHE$_1$(E$_2$)-1-N7Gua, 4-hydroxyestrone(estradiol)1-N7Guanine; SCID, severe combined immune depressed; TAM, tamoxifen

☆ Dedicated to Joachim G. Liehr (1942–2003), our colleague, collaborator and friend.

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doi:10.1016/j.bbcan.2006.03.001

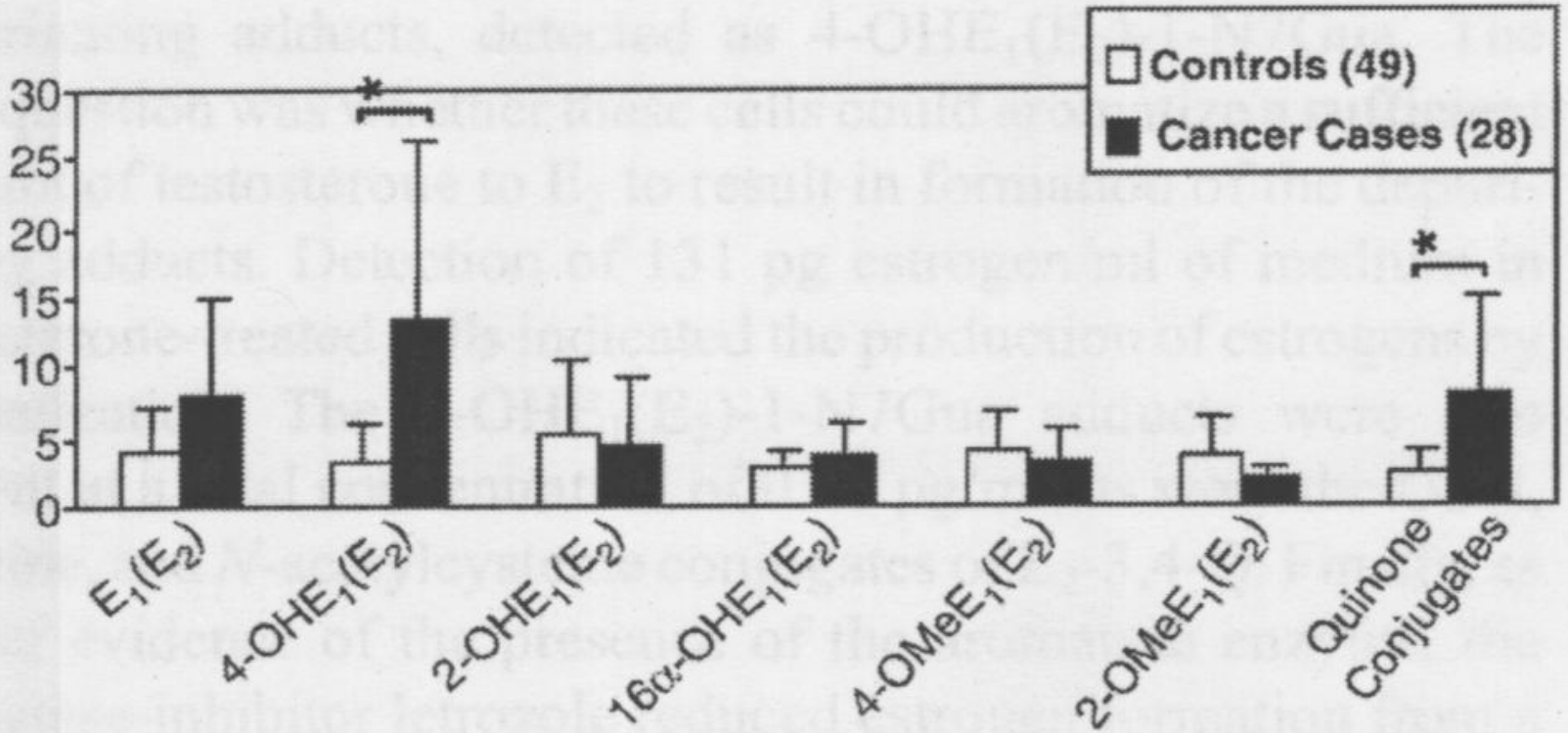

Fig. 2. Relative imbalance of estrogen metabolism in non-tumor breast tissue of women with breast cancer vs. controls. The level of 4-$OHE_1(E_2)$ was significantly higher in cases compared to controls ($P<0.01$). Quinone conjugates were 4-$OHE_1(E_2)$-2-NAcCys, 4-$OHE_1(E_2)$-2-Cys, 2-$OHE_1(E_2)$-(1+4)-NAcCys, and 2-$OHE_1(E_2)$-(1+4)-Cys. The levels of quinone conjugates were significantly higher in cases than in controls ($P<0.003$). *Statistically significant differences were determined using the Wilcoxon rank sum test.

- “In the in vitro transformation of human breast epithelial cells (HBEC) by E_2 or 4-OHE_2, a 5-bp deletion in TP53 exon 4 of chromosome 17 (marker TP53-Dint located in exon 4 of TP53) was also reported…”
- “In addition, BRCA1/2-related inherited breast cancers also show similarly increased frequencies of A.T to G.C mutations and hotspots at several codons of the p53 gene, including codon.”

Chapter 3: Endogenous Estrogens as Carcinogens Through Metabolic Activation

James D. Yager

A common thread linking the main risks for developing breast cancer in women is cumulative, excessive exposure to estrogen. The standard paradigm to account for this association focuses on increased cell proliferation caused by estrogen through estrogen receptor-mediated signal transduction accompanied by increased probability for mutation to occur during DNA synthesis. This chapter provides an overview of the mounting evidence, provided from cell culture and whole animal experimental studies, in support of a role for the oxidative metabolites of estrogen, in particular, the catechol estrogens, in the development of estrogen carcinogenesis. This provides a paradigm for how estrogens may contribute to th
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nyl estradiol is a strong promoter of hepatocarcinogenesis in the rat. Increased oxidative DNA damage has been detected in target tissues after estrogen treatment in both animal model systems. Furthermore, several recent molecular epidemiologic studies have found that a polymorphism associated with a low-activity form of catechol-*O*-methyltransferase, an enzyme involved in the inactivation of catechol estrogens, is associated with an increased risk for developing breast cancer. The increased risk is observed in certain women, although the studies are not consistent on which subgroup of women (e.g., premenopausal or postmenopausal) is at increased risk, and one study detected no increased risk. Reasons for such discrepancies are discussed in light of factors, such as genetic polymorphisms and environmental/lifestyle susceptibility factors, which control the tissue-specific balance within cells among the estrogen metabolites. It is concluded that such factors will have to be identified through additional mechanistic studies and that, as they are identified, they can be incorporated into future molecular epidemiologic studies designed to determine their actual impact on cancer risk in human populations. [J Natl Cancer Inst Monogr 2000;27:67–73]

For a substantial fraction of breast cancer cases in women, well-established risk factors, revealed by epidemiologic studies, include early age at menarche, late first full-term pregnancy, nulliparity, late menopause, family history of breast cancer, socioeconomic status, and perhaps estrogen replacement therapy *(1–5)*. A common thread linking these factors is cumulative, excessive lifetime exposure to estrogen, suggesting that this exposure has an important role in the cause of breast cancer. Although a number of environmental chemicals are suspected of contributing to breast cancer, no single environmental chemical has been identified as a strong "smoking gun" for causing breast cancer *(6)*. However, a consequence of excessive estrogen exposure may include unwanted cell division. The standard paradigm providing a general mechanistic explanation for the association of cumulative, excessive estrogen exposure and breast cancer risk was aptly stated by Feigelson and Henderson *(4)* and is shown in Fig. 1. The notion is that the proliferative stimulus provided by 17β-estradiol (E_2) leads to the appearance of spontaneous mutations; thus, the key contribution of E_2 is the stimulation of breast epithelial cell proliferation (Chapter 8). How-

are able to form direct adducts with DNA *(15)* and/or can cause oxidative damage to lipids *(16)* and DNA through redox cycling processes that produce reactive oxygen species (ROS) [*(7, 8);* Chapter 4]. Increased production of ROS could also lead to disruption of cellular redox homeostasis and, as a consequence, could alter transcription factor function, causing inappropriate alterations in the regulation of gene expression *(17)*.

The possible contribution of these metabolites to estrogen carcinogenesis has received relatively little attention compared with that given to estrogen receptor-mediated processes. However, accumulating evidence, much of which was presented in this symposium, supports an expansion of the standard mechanistic paradigm for the causal association of estrogen exposure and breast cancer (Fig. 1). Thus, while estrogen-induced cell proliferation undoubtedly has an important role in estrogen carcinogenesis, complementary pathways involving indirect and/or direct genotoxicity originating from estrogen metabolites, in particular, the 4-hydroxy catechol metabolite, are also likely to make important contributions. Furthermore, since other metabolites, such as 2-methoxyE_2, may have protective effects, a balance among these metabolites is likely required to maintain homeostasis.

In this chapter, I will provide a brief overview of some evidence in support of a role for estrogen metabolites in estrogen

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See "Notes" following "References."

Yager JD. Chapter 3: Endogenous estrogens as carcinogens through metabolic activation, *J Nat Canc Instit Monographs*, No. 27, pp. 67-73, 2000.

Standard Paradigm

Estrogen, and perhaps progesterone "...affect the rate of cell division and thus manifest their effect on the risk of breast cancer by causing proliferation of breast epithelial cells. Proliferating cells are susceptible to genetic errors during DNA replication which, if uncorrected, can ultimately lead to a malignant phenotype."
(Feigelson and Henderson, Carcinogenesis, 17:2279-84, 1996)

Modified Paradigm

While estrogen-induced cell proliferation undoubtedly has important role in the carcinogenic process, mounting evidence supports a complimentary pathway involving:

Indirect and direct **genotoxicity** originating from estrogen metabolites, i.e. **4-OHE$_2$**

- **Indirect: Oxidative DNA damage** via Redox Cycling → **ROS**
- **Direct: Estrogen-quinone DNA adducts**
- **Protective effects**: Perhaps through **2-methoxy catechol estrogen-mediated** growth inhibition, apoptosis and anti-angiogenesis

Estrogen Metabolism and Breast Cancer

A Risk Model

Fritz F. Parl,[a] Sheila Dawling,[a] Nady Roodi,[a] and Philip S. Crooke[b]

Departments of [a]Pathology and [b]Mathematics, Vanderbilt University, Nashville, Tennessee 37232

Oxidative metabolites of estrogens have been implicated in the development of breast cancer, yet relatively little is known about the metabolism of estrogens in the normal breast. We developed an experimental *in vitro* model of mammary estrogen metabolism in which we combined purified, recombinant phase I enzymes CYP1A1 and CYP1B1 with the phase II enzymes COMT and GSTP1 to determine how 17β-estradiol (E_2) is metabolized. We employed both gas and liquid chromatography with mass spectrometry to measure the parent hormone E_2 as well as eight metabolites, that is, the catechol estrogens, methoxyestrogens, and estrogen–GSH conjugates. We used these experimental data to develop an *in silico* model, which allowed the kinetic simulation of converting and identified a subset of women with an increased risk of breast cancer based on their enzyme haplotypes and consequent E_2-3,4-Q production. Our *in silico* model integrates diverse types of data and offers the exciting opportunity for researchers to combine metabolic and genetic data in assessing estrogenic exposure in relation to breast cancer risk.

Key words: **estrogen; metabolism; breast cancer; risk; genotype; model**

Parl FF et al. Estrogen metabolism and breast cancer: A risk model, *Ann NY Acad Sci,* Vol. 1155, pp. 68-75, 2009.

Introduction

Estrogens have long been recognized as the prime risk factor for the development of breast cancer,[1,2] but their assessment has not progressed beyond traditional exposure data, such as age, age at menarche, and age at first live birth. Although valuable in risk calculation, current models of breast cancer risk prediction based on cumulative estrogen exposure do not reflect observations of and data on mammary estrogen metabolism.[3,4] Here we present a novel approach that is based on the molecular analysis of mammary estrogen metabolism.

Carcinogenesis is usually viewed as a stepwise process beginning with genotoxic effects (initiation) followed by enhanced cell proliferation (promotion). In the breast the main estrogen, 17β-estradiol (E_2), is both a substrate for the phase I enzymes cytochrome P50 (CYP) 1A1 and 1B1 and a ligand for the estrogen receptor (ER). In its dual role of substrate and ligand, E_2 has been implicated in the development of breast cancer by the way it simultaneously causes DNA damage via its oxidation products, the 2-OH and 4-OH catechol estrogens, and by how it stimulates cell proliferation and gene expression via the ER. Thus,

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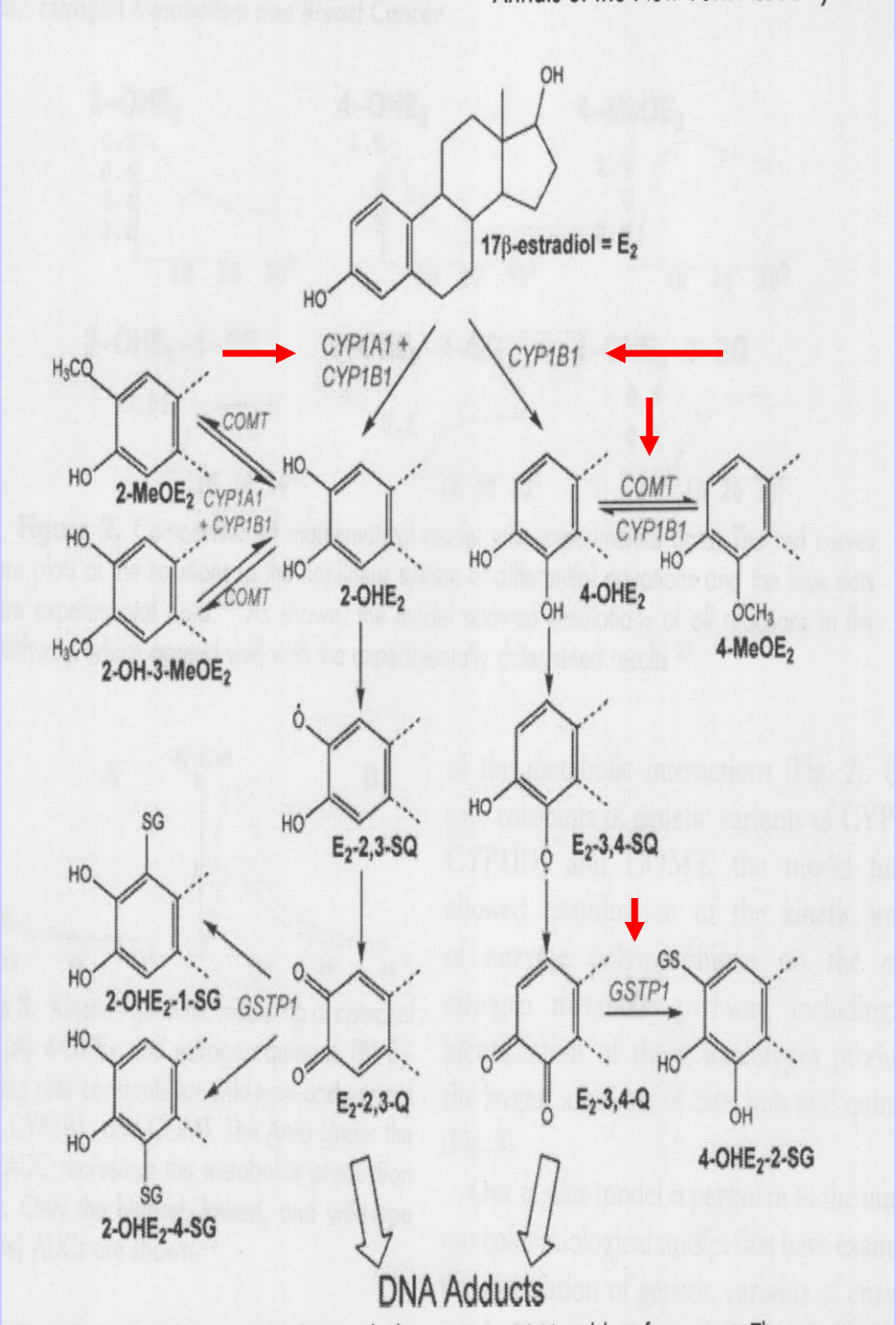
Steroid Enzymes and Cancer: Ann. N.Y. Acad. Sci. 1155: 68–75 (2009).
doi: 10.1111/j.1749-6632.2008.03676.x


17β-estradiol = E2
CYP1A1 + CYP1B1
CYP1B1
COMT
2-MeOE2
CYP1A1 + CYP1B1
COMT
2-OHE2
2-OH-3-MeOE2
COMT
CYP1B1
4-OHE2
4-MeOE2
E2-2,3-SQ
E2-3,4-SQ
GSTP1
2-OHE2-1-SG
GSTP1
E2-2,3-Q
E2-3,4-Q
4-OHE2-2-SG
2-OHE2-4-SG
DNA Adducts

Methylation

Current Drug Metabolism, 2002, *3*, 321-349

Catechol-*O*-Methyltransferase (COMT)-Mediated Methylation Metabolism of Endogenous Bioactive Catechols and Modulation by Endobiotics and Xenobiotics: Importance in Pathophysiology and Pathogenesis

Bao Ting Zhu*

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Abstract: The metabolic *O*-methylation of endogenous catecholamines and other catechols catalyzed by catechol-*O*-methyltransferase (COMT; EC 2.1.1.6) was first described by Dr. Julix Axelrod and his colleagues almost half a century ago. In the past several years, research interest in this catechol-metabolizing system has been renewed because of its potential pathophysiological and pathogenic significance in estrogen-induced hormonal cancers, in the development of degenerative brain disorders, as well as in the development of cardiovascular diseases. In this review paper, I provide a bri
following three areas: **(i)** th
(mainly *S*-adenosyl-*L*-hom
phytochemicals; **(ii)** decreas
for the development of neu
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of the COMT-catalyzed *O*-
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1. INTRODUCTION

The enzymatic *O*-methylation o
amines and other catechols was first
Axelrod and his colleagues almost h
The enzyme that catalyzes their
catechol-*O*-methyltransferase (COMT
uses *S*-adenosyl-*L*-methionine (SAM
The physiological substrates of C
variety of organic chemicals, su
(dopamine, norepinephrine, and
estrogens, dihydroxyindolic intermed
many others [3-7]. In addition, mar
such as triphenols and substituted
isoprenaline, rimiterol, levodopa, benserazide, dihydroxyphenyl serine, and dihydroxy derivatives of tetrahydroxyisoquinolones, are also substrates of COMT [3,4,6,7]. A few recent studies demonstrated that several dietary phytochemicals such as bioflavonoids and tea catechins are exceptionally good substrates for the COMT-mediated *O*-methylation, with metabolic rates much higher than endogenous catecholamines and catechol estrogens [8-11].

It has been a long-held view that the major physiological function of the COMT metabolic system is primarily for the

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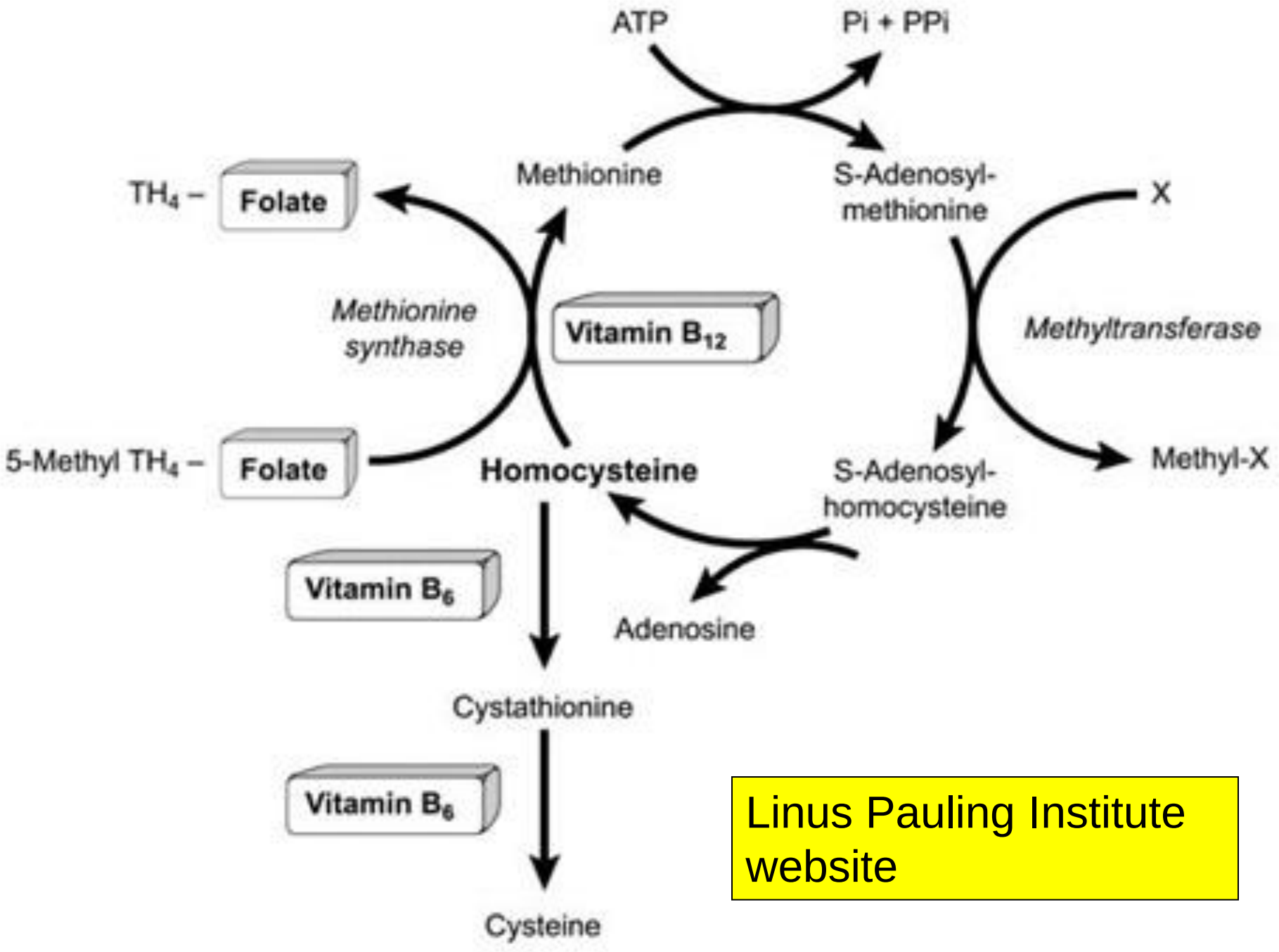
be true in the brain: COMT may modulate the neurotransmitter functions of dopamine and norepinephrine in various mental processes through altering the rate of their metabolic inactivation in different parts of the brain.

In the past several years, research interest in the COMT metabolic system has been renewed as a result of exciting recent developments regarding its potential pathophysiological or pathogenic significance in estrogen-induced hormonal cancers, in the development of degenerative brain disorders such as Parkinson's and Alzheimer's diseases, as well as in the development of a variety of cardiovascular diseases. In this article, I provide a brief overview of this catechol-metabolizing system, with a particular focus on some of the recent developments in these as well as other related areas. Some unifying hypotheses are also discussed with the hope that they will assist us in understanding the

1389-2002/02 $35.00+.00

Zhu BT. Catechol-O-Methyltransferase (COMT)-mediated methylation metabolism of endogenous bioactive catechols and modulation by endobiotics and xenobiotics: Importance to pathophysiology and pathogenesis, *Curr Drug Metab*, Vol. 3, pp. 321-349, 2002

- “The physiological substrates of COMT include a wide variety of organic chemicals, such as catecholamines (dopamine, norepinephrine, and epinephrine), catechol estrogens, dihyroxyindolic intermediates of melanin, and many others.”
- “In addition, many medicinal products, such as triphenols and substituted catechols, dobutamine, isoprenaline, rimiterol, levodopa, benserazide, dihydroxyphenyl serine, and dihydroxy derivatives of tetrahydroxyisoquinoloines are also substrates of COMT.”



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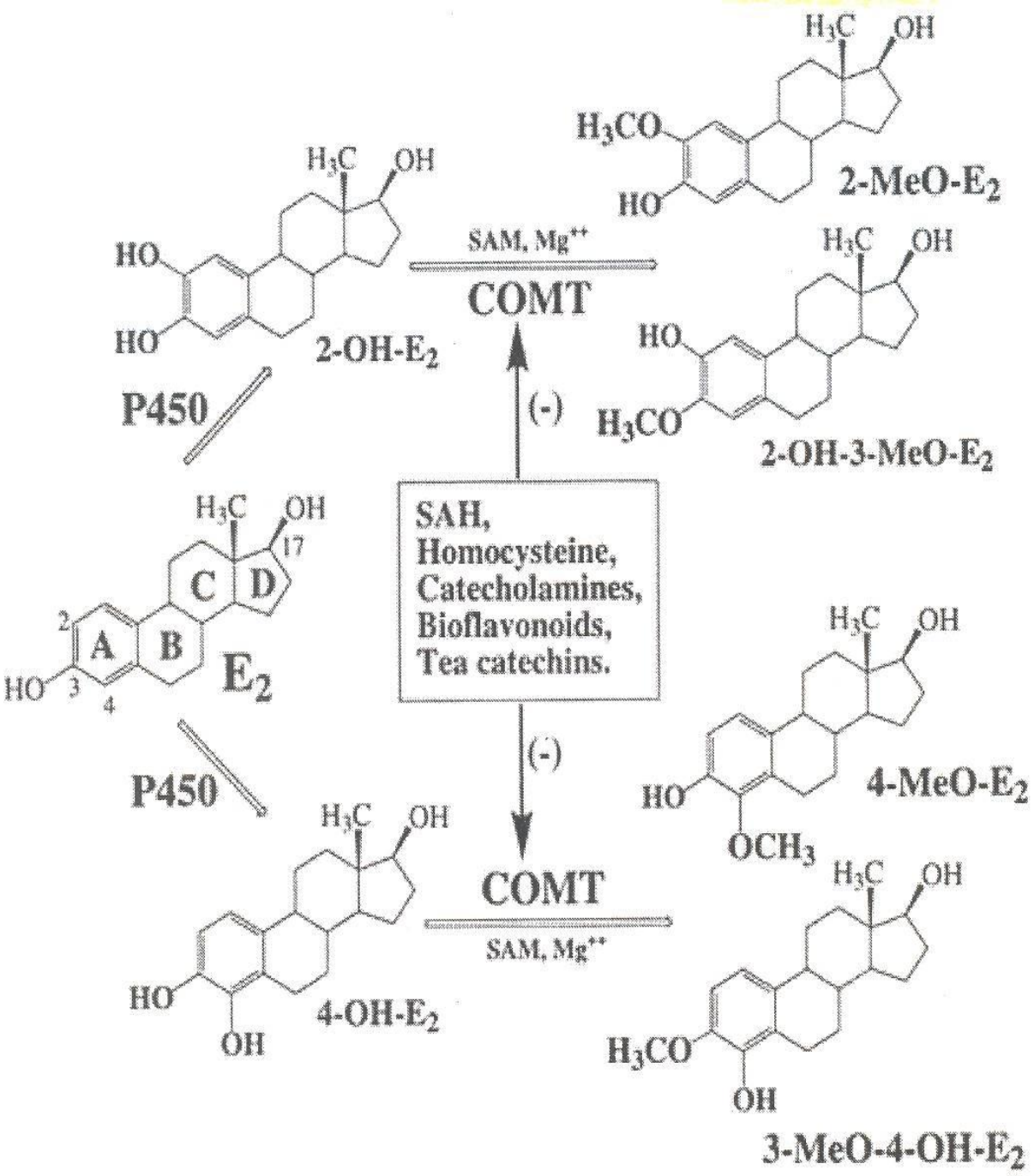
2-MeO-E2
SAM, Mg++
COMT
2-OH-E2
P450
(-)
2-OH-3-MeO-E2
SAH,
Homocysteine,
Catecholamines,
Bioflavonoids,
Tea catechins.
E2
(-)
P450
4-MeO-E2
COMT
SAM, Mg++
4-OH-E2
3-MeO-4-OH-E2

INTERNATIONAL JOURNAL OF ONCOLOGY 22: 499-508, 2003

Medical hypothesis: Hyperhomocysteinemia is a risk factor for estrogen-induced hormonal cancer

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Received August 28, 2002; Accepted October 14, 2002

Abstract. A novel mechanistic hypothesis is proposed which suggests that hyperhomocysteinemia is a risk factor for the development of estrogen-induced hormonal cancer in humans. Mechanistically, hyperhomocysteinemia may exert its pathogenic effects largely through metabolic accumu
cellular *S*-adenosyl-*L*-homocysteine, a strong n
inhibitor of the catechol-*O*-methyltransfe
methylation metabolism of endogenous a
catechol estrogens (mainly 2-hydroxyestradiol
estradiol). While a strong inhibition of th
metabolism of 2-hydroxyestradiol would
formation of 2-methoxyestradiol (an antitum
genous metabolite of 17ß-estradiol), an in
methylation of 4-hydroxyestradiol would lead t
of this hormonally-active and strongly pr
catechol estrogen metabolite. Both of these e
from inhibition of the methylation metaboli
estrogens would facilitate the development of es
hormonal cancer in the target organs. This h
predicts that adequate dietary intake of folate,
vitamin B_{12} may reduce hyperhomocysteine
risk for hormonal cancer. Experimental studie
to determine the relations of hyperhomocystei
altered circulating or tissue levels of 4-hydro
2-methoxyestradiol and also with the altered risk for estrogen-induced hormonal cancer.

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E-mail: btzhu@cop.sc.edu

Abbreviations: COMT, catechol-*O*-methyltransferase; SAM, *S*-adenosyl-*L*-methionine; SAH, *S*-adenosyl-*L*-homocysteine; ER, estrogen receptor; E_2, 17ß-estradiol; E_1, estrone; 2-OH-E_2, 2-hydoxyestradiol; 4-OH-E_2, 4-hydroxyestradiol; 2-MeO-E_2, 2-methoxyestradiol

Key words: hyperhomocysteinemia, estrogen, hormonal cancer

Contents

diseases on the basis of increased oxidative metabolism of endogenous catecholamines to cytotoxic quinones/semiquinones and oxyradicals.

A few recent studies have also reported that the amount of dietary intake of vitamins B_6, B_{12}, and folic acid (which are key cofactors directly involved in homocysteine catabolism) was somewhat correlated with the risk for developing human breast cancer (17-26). Notably, although increased incidence of hormonal cancer has not been reported in patients with hereditary hyperhomocysteinemia, this might have been largely due to the fact that these patients usually die at a very early age before the cancer is fully developed. Here I propose a mechanistic hypothesis, on the basis of currently available experimental evidence, that hyperhomocysteinemia is an important risk factor for the development of estrogen-induced hormonal cancer. This mechanistic hypothesis suggests that hyperhomocysteinemia exerts its pathogenic effects largely through metabolic accumulation of intracellular SAH, a strong non-competitive inhibitor of the COMT-mediated methylation metabolism of endogenous and exogenous catechols (including 2-OH-E_2 and 4-OH-E_2). While a strong

Zhu BT. Medical hypothesis: hyperhomocysteinemia is a risk factor for estrogen-induced hormonal cancer, *Int J Oncol*, Vol. 22, No. 3, pp. 499-508, March 2003

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MOLECULAR PHARMACOLOGY, 56:31–38 (1999).

Characterization and Implications of Estrogenic Down-Regulation of Human Catechol-*O*-Methyltransferase Gene Transcription[1]

TAO XIE, SHU-LEONG HO, and DAVID RAMSDEN

Division of Neurology, University Department of Medicine, University of
Department of Medicine, University of Birmingham, Queen Elizabeth Ho

Received December 11, 1998; accepted March 31, 1999

ABSTRACT

Catechol-*O*-methyltransferase (COMT, EC 2.1.1.6) is a ubiquitous enzyme that is crucial to the metabolism of carcinogenic catechols and catecholamines. Regulation of human COMT gene expression may be important in the pathophysiology of various human disorders including estrogen-induced cancers, Parkinson's disease, depression, and hypertension. The gender difference in human COMT activity and variations in rat COMT activity during the estrous cycle led us to explore whether estrogen can regulate human COMT gene transcription. Our Northern analyses showed that physiological concentrations of 17-β-estradiol (10^{-9}–10^{-7} M) could decrease human 1.3-kilobase COMT mRNA levels in MCF-7 cells in a time- and dose-dependent manner through an estrogen receptor-dependent mechanism. Two DNA fragments immediately 5′ to the published human COMT gene proximal and distal promoters were cloned. Sequence analyses revealed several half-palindromic

Catechol-*O*-methyltransferase (COMT) is a ubiquitous enzyme that catalyzes the transfer of the methyl group from the coenzyme *S*-adenosyl-L-methionine (SAM) to one of the hy- are encoded by two transcripts [1.3 and 1.5 kilobase (kb) in human] regulated by the proximal and distal promoters, respectively (Tenhunen et al., 1994). The structural differ-

Shu-Leong TX & Ramsden D. Characterization and implications of estrogenic down-regulation of human catechol-O-Methyltransferase gene transcription, *Mol Pharm*, Vol. 56, pp. 31-38, 1999.

"Our findings provide the first evidence and molecular mechanism for estrogen to inhibit COMT gene transcription, which may shed new insight into the role of estrogen in the pathophysiology of different human disorders."

Chem. Res. Toxicol. **2004,** *17,* 512−520

Equine Catechol Estrogen 4-Hydroxyequilenin Is a More Potent Inhibitor of the Variant Form of Catechol-*O*-Methyltransferase

Yan Li,[†] Jiaqin Yao,[†] Minsun Chang,[†] Dejan Nikolic,[†] Linning Yu,[†] James D. Yager,[‡] Andrew D. Mesecar,[§] Richard B. van Breemen,[†] and Judy L. Bolton*,[†]

Department of Medicinal Chemistry and Pharmacognosy (M/C 781), College of Pharmacy, University of Illinois at Chicago, 833 South Wood Street, Chicago, Illinois 60612, Division of Toxicological Sciences, Department of Environmental Health Sciences, Johns Hopkins University Bloomberg School of Public Health, 615 North Wolfe Street, Baltimore, Maryland 21205, and Center for Pharmaceutical Biotechnology (M/C 870), College of Pharmacy, University of Illinois at Chicago, 900 South Ashland Avenue, Chicago, Illinois 60607

Received November 26, 2003

Catechol-*O*-methyltransferase (COMT) plays an important role in the inactivation of biologically active and toxic catechols. It has been shown that COMT is genetically polymorphic with a wild-type and variant form where a valine has been substituted with a methionine. Several, but not all, epidemiological studies have shown that women, homozygous with the variant form, have an increased risk of developing breast cancer. Previously, we showed that 4-hydroxyequilenin (4-
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Li Y et al. Equine catechol estrogen 4-hydroxyequilenin is a more potent inhibitor of the variant form of catechol-O-methyltransferase, *Chem Res Toxicol*, Vol. 17, No. 4, pp. 512-20, April 2004

Introduction

COMT[1] (EC 2.1.1.6) catalyzes the transfer of a methyl group from the donor SAM to a catechol substrate (*1*). In mammals, COMT is widely distributed in brain and peripheral tissues (*2*). The physiological substrates of COMT include a wide variety of chemical compounds such as catecholamine neurotransmitters and endogenous and exogenous catechol estrogens (*3*, *4*). It has been a long-held view that the major physiological function of the COMT is primarily for the inactivation of biologically active and toxic endogenous and/or exogenous catechols (*1*). There are two forms of COMT, S-COMT and MB-COMT, which are encoded by a single gene with different transcription start sites. S-COMT is the predominantly expressed form in most human tissues (*5*). COMT activity varies among individuals (*6*), and the level of COMT enzyme activity is genetically polymorphic with a trimodal distribution of low, intermediate, and high levels of activity in red blood cells and liver (*7*). This genetic polymorphism results in 3−4-fold differences in COMT activity (*7*). More recently, it was found that both

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[§] Center for Pharmaceutical Biotechnology (M/C 870), University of Illinois at Chicago.

[1] Abbreviations: DTT, dithiothreitol; ESI MS, electrospray ionization mass spectrometry; GST, glutathione *S*-transferase; MB-COMT, membrane-bound catechol *O*-methyltransferase; PBS, phosphate-buffered saline; PCR, polymerase chain reaction; 2-MeOE$_2$, 2-methoxyestradiol; 4-MeOE$_2$, 4-methoxyestradiol; 4-MeOEN, 4-methoxyequilenin; 2-OHE$_2$, 2-hydroxyestradiol; 4-OHE$_2$, 4-hydroxyestradiol; 4-OHEN, 4-hydroxyequilenin; SAM, *S*-adenosyl-L-methionine; S-COMT, soluble catechol-*O*-methyltransferase; SDS−PAGE, sodium dodecyl sulfate−polyacrylamide gel electrophoresis.

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Published on Web 03/06/2004

- “Known risk factors for women developing breast cancer are associated with estrogen exposure including long-term estrogen-replacement therapy.”
- “4-OHEN is the major phase I catechol metabolite of the equine estrogens equilenin and equilin, which can constitute about 50% of the most widely prescribed estrogen replacement formulation, Premarin.”

- ***"Taken together, the variant form of COMT might be more susceptible to 4-OHEN-mediated inhibition resulting in reduced endogenous and exogenous catechol estrogen clearance in cells, thus prolonging their ability to cause toxicity."***

Estrogenic Phenol and Catechol Metabolites of PCBs Modulate Catechol-O-Methyltransferase Expression *Via* the Estrogen Receptor: Potential Contribution to Cancer Risk

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Abstract: Commercial PCB mixtures have been shown to induce liver tumors in female rats and this effect has been attributed to the effects of PCBs on estrogen metabolism. Catechol metabolites of PCBs are potent inhibitors of COMT activity and are likely to contribute significantly to reduced clearance of genotoxic catechol metabolites of estrogen. The effect of PCB metabolites on COMT expression in cultured cells was investigated to explore potential mechanisms by which PCB exposure alters catechol estrogen clearance. We hypothesize that estrogenic PCB metabolites may contribute to reduction of COMT expression via interaction with the estrogen receptor. To test this hypothesis, human MCF-7 cells were exposed to PCB analogues and the expression of COMT determined. Western blot analysis demonstrated that COMT protein levels were statistically significantly reduced by both the phenolic and the catechol compounds, an effect which was abolished by the anti-estrogen, ICI182780. The above suggests that COMT levels may be reduced by estrogenic PCB metabolites, via interactions between PCB metabolites and the ER. It supports the hypothesis that both phenolic and catechol metabolites of PCBs may contribute to PCB-mediated carcinogenesis through reduction of COMT levels and activities and subsequent reduction in clearance of endogenous and xenobiotic catechols.

Keywords: COMT, carcinogenesis, xenobiotic catechols, PCB; estrogen.

Ho PWL et al. Estrogenic phenol and catechol metabolites of PCBs modulate catechol-O-methyltransferase expression via the estrogen receptor: Potential contribution to cancer risk, *Curr Drug Metab*, Vol. 9, pp. 304-309, 2008

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liver tumors in female rats [9,10] and this effect was tentatively attributed to the effects of PCBs on the biotransformation of estrogen to catechol metabolites.

Catechol metabolites of estradiol (catechol estrogens) are potent signalling molecules [11] and are hypothesized to be central to estrogen-linked carcinogenesis [12-20]. Catechol estrogens, once further oxidized, are capable of metabolic redox cycling between quinone and hydroquinone forms, resulting in free radical generation. Several types of direct and indirect free radical-mediated DNA damage are induced by estrogens *in vitro* and *in vivo*. Among these are: DNA single strand breaks; 8-hydroxylation of guanine; DNA adduct formation by malondialdehyde, a decomposition product of free radical-induced lipid peroxides [21-24]. Catechol estrogens may also induce significant genotoxicity by direct formation of DNA base adducts [13,17].

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but its regulation is poorly understood. However, the estrogen receptor contributes to regulation of COMT expression [36,37].

We hypothesized that catechol and phenolic metabolites of PCBs contribute to estradiol-mediated carcinogenesis not only through reduction of COMT activity and but also its expression. The present studies were conducted to explore this hypothesis, particularly to determine the effect of model estrogenic phenolic and catechol PCB metabolites on the expression of COMT.

MATERIALS AND METHODS

Materials

Where possible, all test reagents and chemicals used in the synthesis of non-commercially available PCBs were purchased from Aldrich Chemical Company, (Milwaukee, WI, USA). Dithiothreitol (DTT), 17β-estradiol (E2), charcoal-stripped bovine calf serum, aprotonin, leupeptin, phenylmethylsulfonyl fluoride, HEPES, $MgCl_2$ and KCl were purchased from Sigma Chemical Co. (St. Louis, USA). MCF-7 cells (human breast adenocarcinoma; ATCC HTB-22), were obtained from the American Type Culture Collection (Rockville, MD). Dulbecco's modified Eagle's medium (DMEM) with or without phenol red indicator, penicillin, strepto-

Indian Journal of Experimental Biology
Vol. 44, August 2006, pp. 597-617

Review Article

Environmental contaminants in pathogenesis of breast cancer

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This review is an attempt to comprehend the diverse groups of environmental chemical contaminants with a potential for pathogenesis of breast cancer, their probable sources and the possible mechanisms by which these environmental contaminants act and interplay with other risk factors. Estrogens are closely related to the pathogenesis of breast cancer. Oxidative catabolism of estrogen, mediated by various cytochrome P450 enzymes, generates reactive free radicals that can cause oxidative damage. The same enzymes of estrogenic metabolic pathways catalyze biological activation of several environmental (xenobiotic) chemicals. Xenobiotic chemicals may exert their pathological effects through generation of reacti
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dependent mitochondrial dysfunction. Many of the environmental pollutants suppress the immune system, which are implicated to risk. A better understanding about the biological effects of different environmental carcinogenic compounds and determination of their impact on rising incidence of breast cancer will be beneficial in improving preventive policy against breast cancer.

Keywords: Aryl hydrocarbon receptor, Breast cancer, Immunotoxicant, Oxidative metabolism, Xenoestrogens

Breast cancer is the most commonly occurring neoplastic disease in women worldwide and is second only to lung cancer as a cause of cancer death in women[1]. There is a gradual increase in breast cancer incidence in most developed countries and in societies which became westernized recently or are in the process. Breast cancer is the second most common cancer among Indian women; however, it is the leading cancer in Mumbai and Kolkata, and an increasing incidence has been recorded in urban females[2,3]. Among the population based cancer registries functioning in various parts of the country (India), the Mumbai Registry is a highly efficient system; and a major portion of the country's epidemiological data have been derived from Mumbai. However, aspects related with different environmental risk factors are not clear in those published reports. Studies on Mumbai population showed highest breast cancer incidence rates among Parsis and Christians, followed by Hindus and Muslims, and lowest rates among Jains and Buddhists[2,4,5]. Interestingly, data from most of the registries indicate that Christians in India have the

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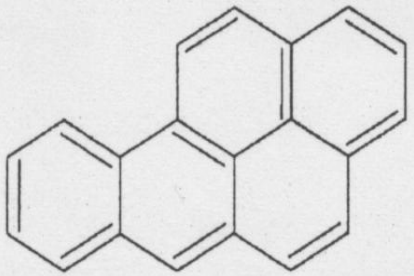
Mukherjee S et al. Environmental contaminants in the pathogenesis of breast cancer, *Indian J Experimental Biol*, Vol. 44, pp. 597-617, August 2006



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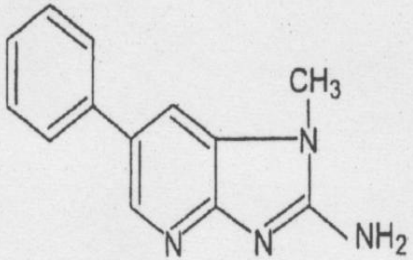

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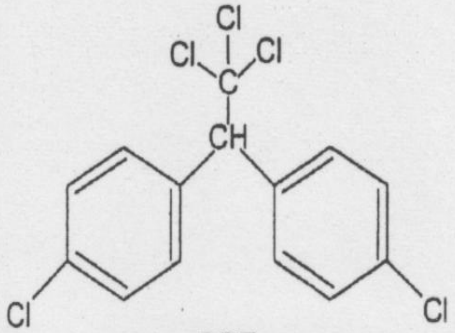

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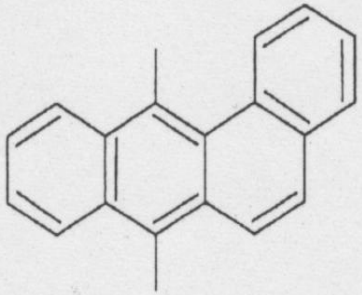

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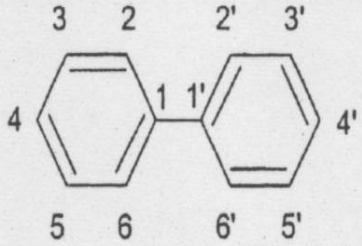
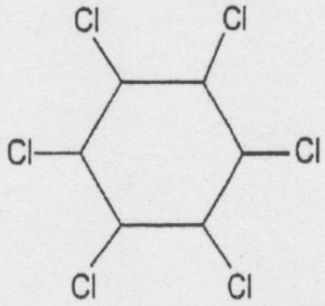
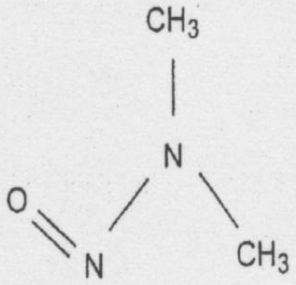


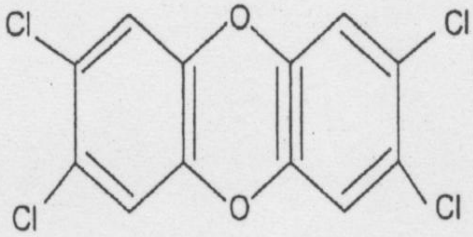
Common backbone-structure of PCBs wherein some or all hydrogen-atoms, attached with carbons 2-6 and 2'-6', can be replaced by chlorine-atoms.



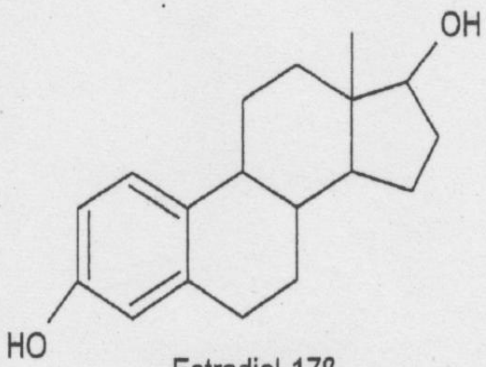
Hexachlorocyclohexane (HCH)



N- nitrosodimethylamine (NDMA)



2,3,7,8-TCDD



Estradiol-17ß

Fig. 3—Selected environmental carcinogens along with estrogen (usually, these chemicals have a structural similarity with estrogen).

endocrine disruptors is a challenging field identifying

Table 3— Man-made chemicals which can act as endocrine disruptors (related with estrogens)

Compound	Principal use/Source	Hormonal character
Atrazine	herbicide	estrogenic
Bisphenol A	manufacture of plastics	estrogenic
Butylhydroxyanisole	manufacture of plastics	estrogenic
Cyclotetrasiloxanes	rubber, plastics, and shampoo	hormonal modulator
DDT	insecticide	estrogenic
Dieldrin	pesticide	estrogenic
DES	synthetic estrogen/drug	estrogenic
Endosulphan	pesticide	estrogenic
Ethynylestradiol	synthetic estrogen/drug	estrogenic
Fenarimol	fungicide	anti-steroid
Hexachlorophene	disinfectant	anti-estrogenic
Kepone	insecticide	estrogenic
4-MBC	organic sun screen	estrogenic
Methoxychlor	insecticide	estrogenic
Menadione	synthetic vitamin K (K3)	anti-estrogenic
Nonylphenol	manufacture of rubber and plastics	estrogenic
o-phenyl phenol	fungicide, dye, rubber and disinfectant	estrogenic
Phthalates	plastics, fixatives for perfume	estrogenic
Pentachlorophenol	pesticide and wood preservative	anti-estrogenic
PCBs	plasticizers, dyes and coolants	estrogenic
PAHs	burning of organic substances	anti-/estrogenic
Triphenyltin	algicides and molluscicides	steroid inhibitor
Toxaphene	insecticide	estrogenic
Vinclozolin	fungicide	anti-steroid

Table 5—Selected pesticides categorized by chemical class

Insecticides	
Carbamate:	carbaryl, carbosulfan, pirimicarb, aldicarb, methomyl, oxamyl, methiocarb
Organochlorine:	DDT, HCH, lindane, methoxychlor, pentachlorophenol, aldrin, chlordane, dieldrin, endosulfan, endrin, heptachlor:
Organophosphorous:	dichlorvos, monocrotophos, malathion, dimethoate, omethoate, phoxim, chlorpyrifos, diazinon, pirimiphos-methyl, quinalphos, fenitrothion, parathion, parathion-methyl, profenofos, trichlorfon
Pyrethroid:	bioallethrin, deltamethrin, fenpropathrin, fenvalerate, permethrin, sumithrin, cypermethrin
Herbicides	
Amide:	isoxaben, pentanochlor, alachlor, metolachlor, chlorthiamid
Quaternary ammonium (Dipyridyl):	paraquat, diquat
Phenoxy:	2,4-dichlorophenoxy acetic acid (2,4-D), 2,4,5-trichlorophenoxy acetic acid (2,4,5-T), 2,4,5-trichlorophenoxy propionic acid (2,4,5-TP)
Triazine:	atrazine, simazine, cyanazine, atraton
Unclassified group:	oxadiazon, pentachlorophenol

"It has been thought that some pesticides and related chemicals may act as carcinogens. These xenobiotic compounds have been shown to enhance oxidative stress and lipid peroxidation in various tissues, and adversely affect the lymphocyte function."

Table 6—Dietary mutagens, which may have relation with the pathogenesis of breast cancer, and their metabolizing enzymes

Mutagenic chemicals	Principal metabolizing enzymes
Acrylamide and glycidamide	CYP2E1, epoxide hydrolase, GST
Heterocyclic aromatic amines	CYP1A2, NAT, SULT, GST
Polar	
Imidazoquinoline:	
IQ, MeIQ	
Imidazoquinoxaline:	
MeIQx	
Imidazopyridine:	
PhIP	
Non-polar	
Pyridoimidazole/Pyridoindole:	
Trp-P-1, Trp-P-2,	
Glu-P-1, Glu-P-2, AαC	
MeAαC	
***N*-nitrosamines**	CYP2E1, CYP2A6
Volatile	
N-nitrosodimethylamine	
N-nitrosodiethylamine	
N-nitrosopyrrolidine	
N-nitrosopiperidine	
N-nitrosomethyl-benzylamine	
Non-volatile	
N-nitrosoproline	
N-nitrosothiazolidine-4-carboxylic acid	
Polycyclic aromatic hydrocarbons (PAHs)	CYP1A1, CYP1B1, epoxide hydroxylase, GST, glucuronyl transferases
Benzo[a]pyrene	Benzo[b]fluoranthene
Dibenz[a,h]anthracene	
Benzo[b]fluoranthene	
Indeno[1,2,3-cd]pyrene	

Diagnosing specific estrogen metabolism imbalances

2-hydroxyestrone: 16α hydroxyestrone

Metametrix
Clinical Laboratory

4855 Peachtree Industrial Blvd.
Norcross, GA 30092
770-446-5483 Fax: 770-441-2237

Ordering Physician
Metametrix
4855 Peachtree Industrial Blvd.
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0142 Estronex™ - 2/16 OH Estrogen Ratio in Urine — *Methodology: Enzyme Immunoassay, Colorimetric Assay*

2-hydroxyestrone:16α hydroxyestrone ratio - Estronex

	Result	Normal Limits			
		Pre-Menopausal	Post-Menopausal without hormone therapy	Post-Menopausal with hormone therapy	
2-Hydroxyestrogens (2OHE)	20.8	3 - 40	2 - 10	10 - 75	ng/mg crea
16-Hydroxyestrone (16OHE1)	11.7	3 - 30	2 - 8	5 - 25	

Creatinine = 100 mg/dl

The ideal value for the 2/16 ratio is above 2.0. The following have been shown to raise the ratio.

- Cruciferous vegetables (e.g. broccoli, brussel sprouts, cabbage, cauliflower)
- Supplementation of indole-3-carbinol (I-3-C) or diindolylmethane (DIM)
- Soy isoflavones
- Flax seeds (not oil)
- Omega-3-fatty acids (DHA & EPA) found in fish (e.g. mackerel, lake trout, herring, sardines, salmon) and marine algae also may help to lower cancer risk. Assure antioxidant adequacy when adding polyunsaturated oils.

- These guidelines are intended as a starting point for the clinician who requested the test and are based only on the laboratory results included in this report. Final recommendations should be implemented by the clinician with consideration of medical history and current clinical observations.
- These tests are not intended for the diagnosis of specific disorders.

Georgia Lab Lic. Code #067-007
CLIA ID# 11D0255349

New York Clinical Lab PFI #4578
Florida Clinical Lab Lic. #800008124

Laboratory Directors
J. Alexander Bralley, PhD
Robert M. David PhD
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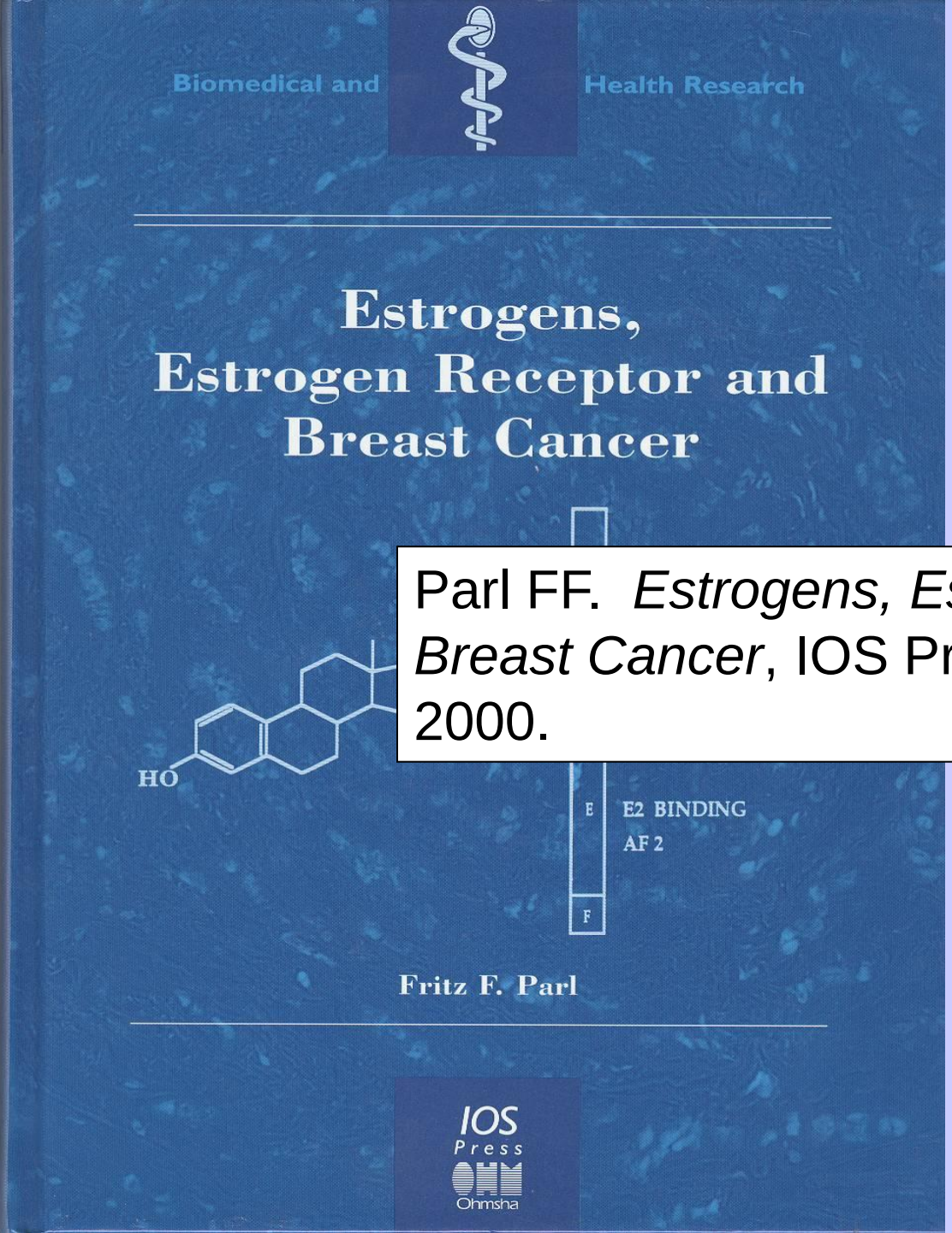

Parl FF. *Estrogens, Estrogen Receptor and Breast Cancer*, IOS Press, Amsterdam, 2000.

- "Reliance on the 2-OHE_1/16α-OHE_1 ratio may be an oversimplification of the significance of 16α-estrogen metabolites in the etiology of breast cancer. By meta-analysis of estrogen metabolism, Lemon et al found that catechol estrogen metabolism rather than C-16α-hydroxylation was highly correlated with breast cancer."

- "Moreover, the C-4 hydroxylation pathway has often been overlooked for technical reasons associated with the difficulty in accurate quantitation of individual catechol estrogens. Since 4-OHE_2 and 4-OHE_1 have been shown to be carcinogenic, determination of the 2-OHE_1/16α-OHE_1 ratio or measurement of total catechol estrogens without distinction between C-2 and C-4 hydroxylated metabolites may be misleading."

24 hour urinary hormone analysis from Meridian Valley Labs

Comparative Measurements of Serum Estriol, Estradiol, and Estrone in Non-pregnant, Premenopausal Women: A Preliminary Investigation

by Jonathan V. Wright, MD,
Brian Schliesman, MCT, and Lynn Robinson, MCT

Abstract

Little to no data exi
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Wright JV et al. Comparative measurements of serum estriol, estradiol, and estrone in non-pregnant, premenopausal women: A preliminary investigation, *Alt Med Rev*, Vol. 4, No. 4, pp. 266-270, August 1999.

Introduction

While reference values are readily available for serum estrone and estradiol, serum estriol levels are listed in reference books for only pregnant women. Figure 1 demonstrates the biosynthesis of estrogens. The conventional medical practice has been to virtually ignore estriol as being an insignificant hormone. Prior to the 1970s, the technology was not sophisticated enough to accurately analyze estriol in non-pregnant patients. By the time estriol could be analyzed accurately, researchers had already conclusively demonstrated that estriol was a much weaker hormone than estradiol and estrone; therefore, it was believed to be of no known consequence.

Because the quantitative research on estriol to date had been focused on concentrations in pregnant women, we concluded that to determine normal serum estriol levels in healthy non-pregnant, premenopausal women, a reliable test needed to be developed.

Jonathan V. Wright, MD - Medical Director, Tahoma Clinic
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Brian Schliesman, MS - Meridian Valley Lab

Lynn Robinson, MLT - Meridian Valley Lab

- “The Estrogen Quotient (EQ), a calculated value illustrating the proportionately large quantity of estriol compared to the sum of estrone and estradiol, was determined by taking the ratio of the total estriol concentration to the sum of the total estrone and estradiol concentrations…”
- “Participant selection criteria for the study was as follows: female, premenopausal, between the ages of 18 and 40, not on birth control or any other steroid hormone medication, and healthy.”
- “The result of these experiments show that serum estriol was always significantly higher than the sum of estrone and estradiol and less fluctuating. We conclude that estriol is probably a significant estrogen component.”

$$\frac{\text{Estriol}}{\text{Estrone + Estradiol}}$$

Treatment options

Optimizing estrogen metabolism

Indole-3-carbinol (I3C)

vs.

Diindolylmethane (DIM)

Pairwise Combinations of Estrogen Metabolism Genotypes in Postmenopausal Breast Cancer Etiology

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[1]Center for Clinical Epidemiology and Biostatistics and Department of Biostatistics and Epidemiology; [2]Abramson Cancer Center; [3]Department of Medicine; [4]Division of Oncology, Children's Hospital of Philadelphia; [5]Fox Chase Cancer Center, Philadelphia, Pennsylvania; and [6]Department of Obstetrics and Gynecology Oregon Health and Science University, Portland, Oregon

Abstract

Estrogen exposures have been associated with breast cancer risk, and genes involved in estrogen metabolism have been reported to mediate that risk. Our goal was to better understand whether combinations of candidate estrogen metabolism genotypes are associated with breast cancer etiology. A population-based case-control study in three counties of the Philadelphia Metropolitan area was undertaken. We evaluated seven main effects and 21 first-order interactions in African Americans and E for genotypes at *COMT, CYP1A1, CYP1A SULT1A1*, and *SULT1E1* in 878 breast ca matched random digit–dialed controls. icans, we observed main effect associ containing any *CYP1A1*2C* (odds ratio, interval, 1.09-2.67) and breast cancer. effects were observed in African America first-order interactions were observed. In European Americans, interactions between *SULT1A1*2* and *CYP1A1*2C* genotypes ($P_{interaction}$ < 0.001) and between *SULT1E1* and *CYP1A2*1F* genotypes were observed ($P_{interaction}$ = 0.006). In African Americans, an interaction between *SULT1A1*2* and *CYP1B1*4* was observed ($P_{interaction}$ = 0.041). We applied the false-positive report probability approach, which suggested that these associations were noteworthy; however, we cannot

Rebbeck TR et al. Pairwise combinations of estrogen metabolism genotypes in postmenopausal breast cancer etiology, *Cancer Epidem Biomarkers Prev,* Vol. 16, No. 3, pp. 444-50, March 2007

Introduction

There is substantial evidence that es associated with breast cancer risk. This the form of endogenous exposures relate or reproductive history (1-3) or exogenou use of hormone replacement therapy established that hormone replacement unopposed estrogen increases breast c combined estrogen-progestin hormone re associated with even higher risks (4).

It can be hypothesized that the meta mediated by inherited genotypes, influenc cancer relationship. The genes involved in the disposition of estrogen are well known, and include catechol-*O*-methyltransferase (*COMT*), progesterone receptor (*PGR*), the sulfotransferases *SULT1A1* and *SULT1E1*, and members of the cytochrome P50 family including *CYP1B1, CYP1A2, CYP1A1*; and *CYP3A4* (Fig. 1; Table 1; ref. 5). There is also support from many studies for the hypothesis that these genes influence breast cancer risk (6-13). Therefore, the combined knowledge of with breast cancer risk in a population-based sample of postmenopausal women.

Materials and Methods

Study Design and Data Collection. The Women's Insights and Shared Experiences study is a population-based case-control study in which incident breast cancer cases and endometrial cancer cases were identified through hospitals and the Pennsylvania State Cancer Registry, and frequency-matched controls were identified from the community using random-digit dialing. Thus, both a breast cancer case-control study and an endometrial cancer case-control study were conducted using similar methods. Additional details of our study design can be found in studies by Bunin et al. (14) and Strom et al. (15) The source population for this study was the three counties of Philadelphia (PA), Delaware (PA), and Camden (NJ). Potentially eligible cases were women residing in these counties at the time of diagnosis who were ages 50 to 79 years old and were newly diagnosed with breast cancer between July 1, 1999, and June 30, 2002. The cases were

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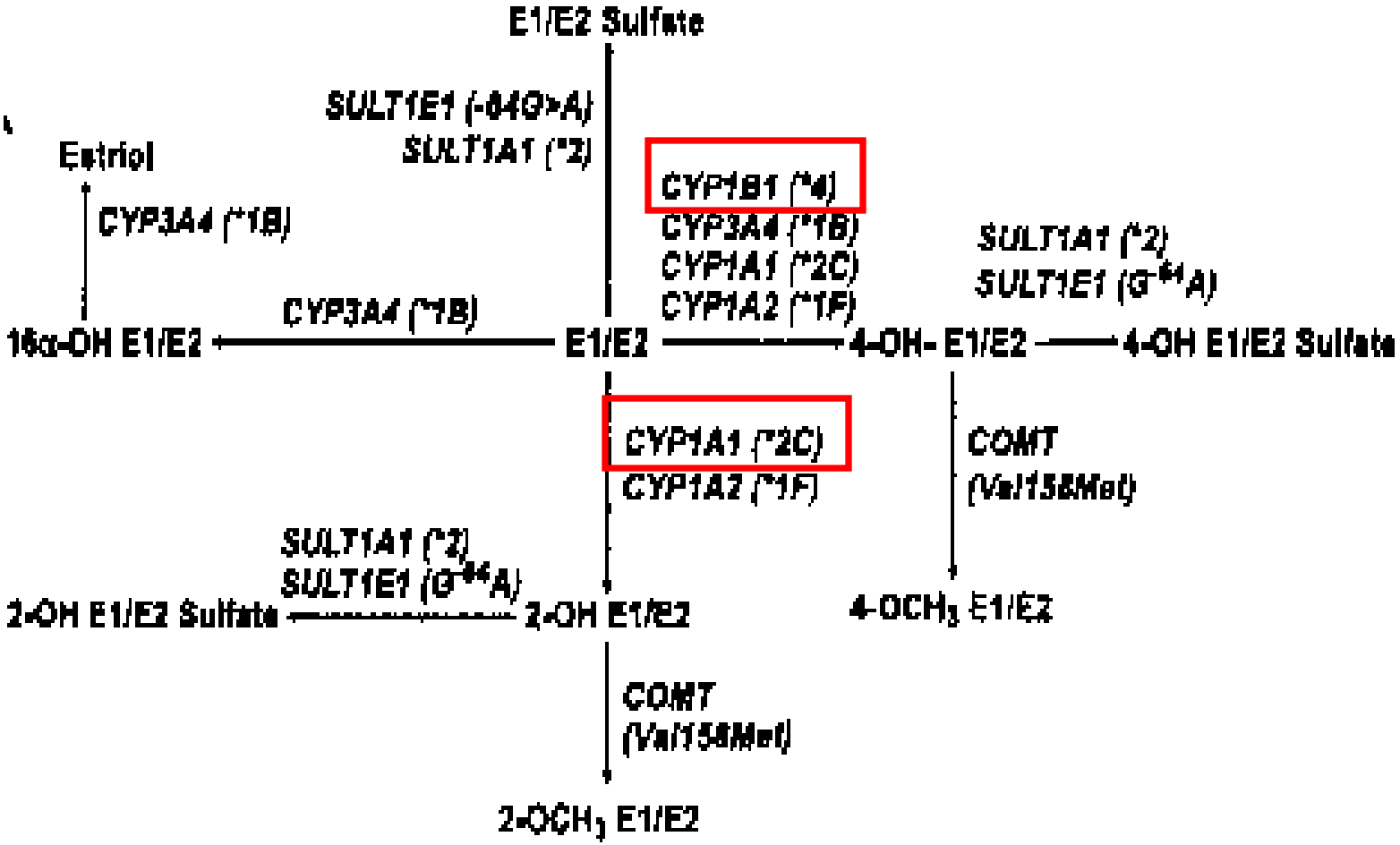

Figure 1. Steroid hormone metabolism pathways with genetic variants studied at these genes shown in parentheses.

Indole-3-Carbinol Is a Negative Regulator of Estrogen[1,2]

Karen J. Auborn,*†**[3] Saijun Fan,*‡ Eliot M. Rosen,*‡††† Leslie Goodwin,* Alamelu Chandraskaren,* David E. Williams,‡‡# DaZhi Chen* and Timothy H. Carter*†§

*North Shore–Long Island Jewish Research Institute, Manhasset, NY 11030, Departments of †Otolaryngology and ‡Radiology, Long Island Jewish Medical Center, Long Island Campus of Albert Einstein College of Medicine, New Hyde Park, NY 11040, Departments of **Microbiology and Immunology and ††Developmental and Molecular Biology, Albert Einstein College of Medicine, Bronx, NY 10461, ‡‡Department of Environmental and Molecular Toxicology and #Linus Pauling Institute, Oregon State University, Corvallis, OR 97331 and §Department of Biological Sciences, St. Johns University, Jamaica, NY 11530

ABSTRACT Studies increasingly indicate that dietary indole-3-carbinol (I3C) prevents the development of estrogen-enhanced cancers and translational studies su I3C causes growth arrest a best use I3C together with the possibility that inductio (DIM), which is the acid-ca undergo apoptosis. We eva I3C/DIM to cause apoptosis was evaluated by real-time sured by a mitochondrial fu assay was used to specifica line was used for these stud thus increasing apoptosis, and genistein, the potential exists for prophylactic or therapeutic efficacy of lower concentrations of each phytochemical when used in combination. J. Nutr. 133: 2470S–2475S, 2003.

KEY WORDS: • *indole-3-carbinol* • *diindolylmethane* • *genistein* • *estradiol*

Indole-3-carbinol (I3C)[4] and its biologically active dimer diindolylmethane (DIM), which are obtained from the dietary consumption of cruciferous vegetables (*Brassicas*), are promising agents for the prevention of estrogen-enhanced cancers. A combination of epidemiological and experimental data provides suggestive evidence that a high intake of cruciferous vegetables protects against some cancers at various sites (1). In a nationwide study of postmenopausal women in Sweden, consumption of cruciferous vegetables was inversely associated with breast cancer risk (2). Although cruciferous vegetables have a number of cancer-preventing compounds, I3C alone shows efficacy for the prevention of breast (3), endometrial (4) and cervical cancers (5) in animal models. Importantly, I3C shows efficacy for treatment of precancerous lesions of the cervix in translational human studies (6).

In estrogen-sensitive cells, I3C/DIM and estrogen have opposing activities on cells. Estrogen promotes tumor growth, whereas I3C suppresses it. For example, the K14-HPV16 mouse, which has transgenes for the oncogenes from human papillomavirus type 16, only develops cervical cancer when estrogen is given chronically (7). However, dietary I3C prevents cervical cancer in these estrogen-treated mice (5). This is consistent with many in vitro studies that show that estrogen increases cell proliferation (8,9) and I3C causes growth arrest (10). Immunohistochemistry studies determined (5) that

[1] Published in a supplement to *The Journal of Nutrition*. Presented at the "Nutritional Genomics and Proteomics in Cancer Prevention Conference" held September 5–6, 2002, in Bethesda, MD. This meeting was sponsored by the Center for Cancer Research, National Cancer Institute; Division of Cancer Prevention, National Cancer Institute; National Center for Complementary and Alternative Medicine, National Institutes of Health; Office of Dietary Supplements, National Institutes of Health; Office of Rare Diseases, National Institutes of Health; and the American Society for Nutritional Sciences. Guest editors for the supplement were Young S. Kim and John A. Milner, Nutritional Science Research Group, Division of Cancer Prevention, National Cancer Institute, Bethesda, MD.

[2] This work is supported by National Institutes of Health grants 2R01-CA733850 (to K. J. Auborn) and R01-CA82599 (to E. M. Rosen). The contents are solely the responsibility of the authors.

[3] To whom correspondence should be addressed. E-mail: kauborn@nshs.edu.

[4] Abbreviations used: BRCA-1, breast cancer 1; DIM, diindolylmethane; DMSO, dimethyl sulfoxide; ER, estrogen receptor; ERE, estrogen receptor element; GADD, growth arrest in response to DNA damage; I3C, indole-3-carbinol; PCNA, proliferating cell nuclear antigen; RT-PCR, reverse transcriptase–polymerase chain reaction; UV, ultraviolet.

JN THE JOURNAL OF NUTRITION

Auborn KJ et al. Indole-3-carbinol is a negative regulator of estrogen, *J Nutr*, Vol. 133, pp. 2470S-2475S, 2003

- “A number of mechanisms exist (that are not mutually exclusive) whereby I3C (or DIM) can diminish the effects of estrogen on tumor growth. First, I3C and DIM induce enzymes such as CYP1A1, which converts estrone to 2-hydroxyestrone and ultimately results in metabolites that are antiproliferative and proapoptotic.”

- “Second, in the case of genes driven by the estrogen receptor (ER)-α, I3C acts as a negative regulator.”

- “Finally, in the absence of estrogen, I3C and DIM induce many genes that have potential to induce growth arrest and apoptosis and therefore might counteract the effects of estradiol.”

The Cruciferous Choice: DIM or I3C? Phytonutrient Supplements for Cancer Prevention and Health Promotion

by Michael A. Zeligs, MD

Abstract

Cruciferous vegetable phytonutrients include natural substances whose supplemental use has great potential for the prevention of human cancer. The additional discovery that the cruciferous indoles, diindolylmethane (DIM®) and indole-3-carbinol (I3C), also promote healthy estrogen metabolism has expanded their usefulness as dietary supplements for many estrogen-related conditions. Beyond cancer prevention, effective uses of absorbable DIM have included benefits for perimenopausal women, in premenstrual syndrome (PMS), in endometriosis, and in cervical dysplasia. Also benefited from supplementation are women on estrogen replacement (HRT), as well as men with estrogen-related conditions including prostate hypertrophy. In choosing dietary supplement formulations containing DIM or I3C, it is important to understand basic differences in their phytochemical characteristics and interaction potential. These differences have important implications as to their relative safety for long-term use.

Introduction to the Cruciferous, Indole Phytonutrients

Cruciferous vegetables (broccoli, cabbage, cauliflower, Brussels sprouts, bok choy) are in the news as powerful sources of cancer-preventive phytonutrition. A recent study of Seattle men showed that three or more servings of cruciferous vegetables a week can reduce prostate cancer risk almost by half.[1] For women however, the news is not so clear. In a large prospective study of 350,000 women, no protection from

on I3C released during digestion. Pure forms of these natural substances

expanding applications in preventive nutrition, their use in women has actually been shown to reduce risk status for breast cancer,[5] and cause the regression and disappearance of advanced cervical dysplasia.[6] The supplemental use of DIM and I3C are under active investigation.[7] These natural products are increasingly available as dietary supplements for healthier estrogen metabolism, perimenopause, men's health and cancer risk-reduction

Significant amounts of DIM are found in cruciferous plants following crushing.[8] This is unlike I3C which, due to its unstable nature, is only transiently present, primarily during digestion.[9] I3C is the natural precursor to DIM, which is formed from a "condensation reaction" in which one I3C molecule combines with another. The resulting DIM is a "di-indole" or double molecule formed from two I3C molecules. Release of active DIM is facilitated by enzymes in the plant and is also due to the action of gastric acid

products, including DIM, after I3C is exposed to stomach acid.[10] When I3C is kept dissolved in water, or buffered in weakly acidic solutions, a greater conversion to DIM occurs. DIM requires a special dietary supplement formulation to provide for improved solubility and complete gastrointestinal absorption. I3C requires careful storage, avoiding heat, moisture and light to slow its rapid breakdown on the shelf. Taken as a dietary supplement, I3C requires gastric acid for conversion to active products. I3C is more irritating to the stomach than DIM, due to its chemical reactivity.[11] I3C is much more sensitive to interaction with components of food, especially vitamin C, which limit its conversion into DIM and other condensation products. Conversion from I3C into DIM not only requires a precise acidity, it requires time. This conversion may proceed slowly, requiring more than a typical intestinal transit time to be complete. ➤

Zeligs MA. The cruciferous choice: DIM or I3C? Phytonutrient supplements for cancer prevention and health promotion, *Townsend Letter for Doctors and Patients*, #217/218, pp. 47-54, August/September 2001.

Aspect Compared	Cruciferous Phytonutrient	
	Absorbable-DIM®	I3C
Activity	fully active	precursor
Absorption	predictable	unpredictable
Stability	high	low
Toxicity	none-reported	dose related, includes dizziness and gastritis
Tumor Promotion	none-reported	positive in rats, promoting colon cancer: relates to excess enzyme induction
Anti-oxidant Action	purely antioxidant	some reaction products like indolocarbazole (ICZ) cause oxidative damage
Relative Dose Needed	3 times dietary intake	30 times dietary intake
Estrogen Regulation	more complete	dose limited, due to toxicity above 400 mg/day
PMS Benefits	demonstrated	untested
Breast Pain Resolution	demonstrated	untested
Cervical Health	demonstrated	demonstrated
Weight Loss Promotion	demonstrated	untested
Drug, Nutrient, Hormone Interaction Potential	limited	greater
Enzyme Induction	limited and specific	greater and non-specific

Lignans and phytoestrogens

The Effect of Flaxseed and Wheat Bran Consumption on Urinary Estrogen Metabolites in Premenopausal Women[1]

Carol J. Haggans, Elsa J. Travelli, Wi
Margaret C. Martini, and Joanne L. S

Department of Food Science and Nutrition, Universi
Minnesota 55108 [C. J. H., E. J. T., M. C. M., J. L. S
Biostatistics, School of Public Health, University of
Minnesota 55455 [W. T.]

Abstract

**Estrogen is metabolized along two con
form the 2-hydroxylated and the 16α-
metabolites. Based on proposed differe
activities, the ratio of these metabolites
hydroxyestrogen:16α-hydroxyestrone (
been used as a biomarker for breast c
with an elevated 2:16α-OHE1 ratio ar
be at a decreased risk of breast cancer
most significant source of plant lignan
an excellent source of dietary fiber, ha
shown to have chemoprotective benefi
benefits may be attributable to their influence on
endogenous sex hormone production and metabolism. We
examined the effect of flaxseed consumption alone and in
combination with wheat bran on urinary estrogen
metabolites in premenopausal women. Sixteen
premenopausal women were studied for four feeding
treatments lasting two menstrual cycles each in a
randomized cross-over design. During the four feeding
treatments, subjects co
supplemented with bak
wheat bran, 10 g of fla
of flaxseed plus 28 g of
excretion of 2-hydroxy
as well as their ratio, 2
enzyme immunoassay.
significantly increased
($P = 0.034$), but wheat
suggest that flaxseed m
premenopausal women.**

Introduction

Strong evidence sugges
breast cancer risk (1–6).

shown to cause cell proliferation and DNA damage in mouse mammary cells (18), to have significant uterotropic activity (15), and to be positively correlated with mammary tumor incidence in mice (19). Recent studies that showed that urinary 16α-OHE1 is positively correlated with bone mass density in postmenopausal women (20, 21) further support its proposed estrogenic activity.

Because of the competing nature of the 2-hydroxylation

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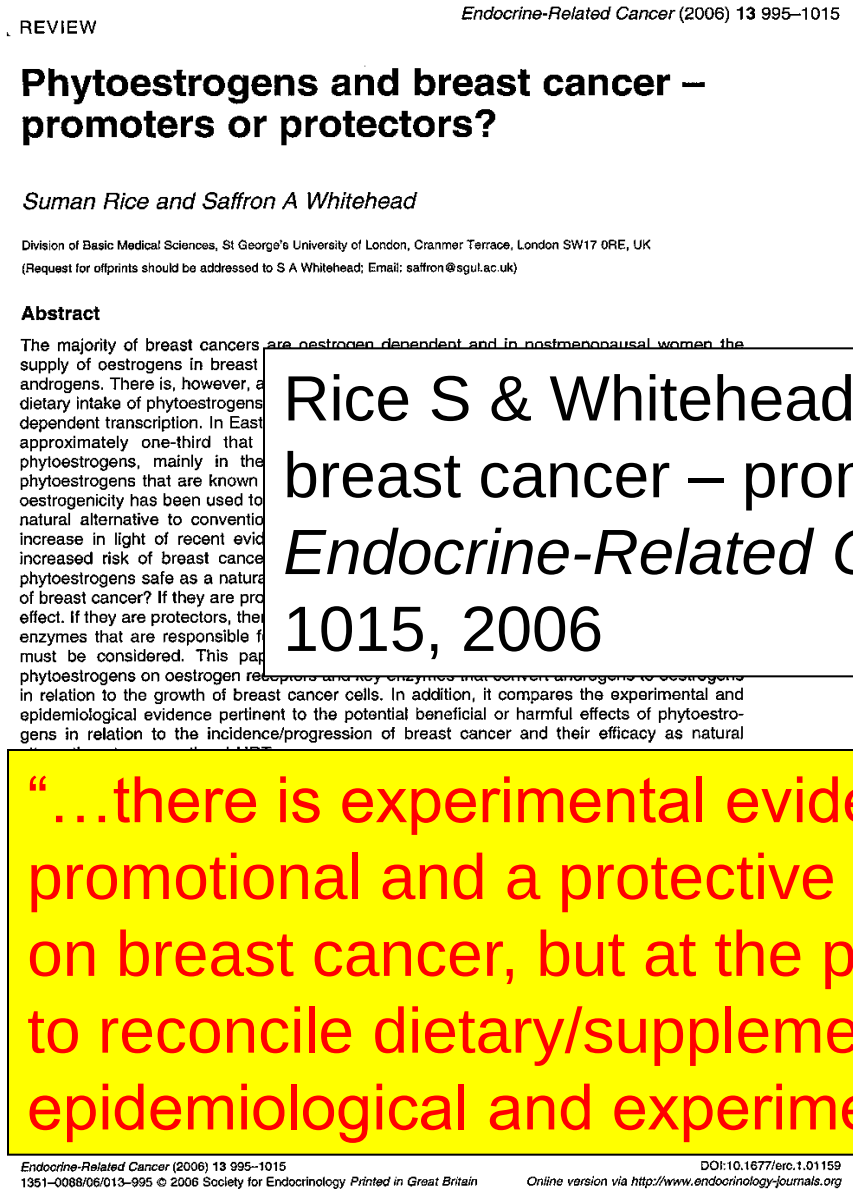
page charges. This article mus
accordance with 18 U.S.C. Sec
[1] Supported by Grant 96-3520
Agriculture and Grant M01-RR
Resources, NIH.
[2] To whom requests for reprints should be addressed, at Department of Food Science and Nutrition, University of Minnesota, 1334 Eckles Avenue, St. Paul, MN 55108.

[3] The abbreviations used are: 2-OHEstrogen, 2-hydroxyestrogen; 2-OHE1, 2-hydroxyestrone; 16α-OHE1, 16α-hydroxyestrone; SHBG, sex hormone-binding globulin; 2:16α-OHE1, 2-hydroxyestrogen:16α-OHE1; LH, luteinizing hormone; BMI, body mass index; Ctrl, control; F, flaxseed; WB, wheat bran; WBF, WB F.

Haggans CJ et al. The effect of flaxseed and wheat bran consumption on urinary estrogen metabolites in premenopausal women, *Cancer Epidemiol Biomarkers Prev*, Vol. 9, pp. 719-23, July 2000.

"Flaxseed supplementation significantly increased the urinary 2:16α-OHE1 ratio , but wheat bran had no effect. These results suggest that flaxseed may be chemopreventive in premenopausal women."



REVIEW

Endocrine-Related Cancer (2006) **13** 995–1015

Phytoestrogens and breast cancer – promoters or protectors?

Suman Rice and Saffron A Whitehead

Division of Basic Medical Sciences, St George's University of London, Cranmer Terrace, London SW17 0RE, UK

(Request for offprints should be addressed to S A Whitehead; Email: saffron@sgul.ac.uk)

Abstract

The majority of breast cancers are oestrogen dependent and in postmenopausal women the supply of oestrogens in breast androgens. There is, however, a dietary intake of phytoestrogens dependent transcription. In East approximately one-third that phytoestrogens, mainly in the phytoestrogens that are known oestrogenicity has been used to natural alternative to conventio increase in light of recent evic increased risk of breast cance phytoestrogens safe as a natura of breast cancer? If they are pro effect. If they are protectors, the enzymes that are responsible f must be considered. This pap phytoestrogens on oestrogen receptors and key enzymes that convert androgens to oestrogens in relation to the growth of breast cancer cells. In addition, it compares the experimental and epidemiological evidence pertinent to the potential beneficial or harmful effects of phytoestrogens in relation to the incidence/progression of breast cancer and their efficacy as natural

Rice S & Whitehead SA. Phytoestrogens and breast cancer – promoters or protectors? *Endocrine-Related Cancer*, Vol. 13, pp. 995-1015, 2006

"…there is experimental evidence for both a promotional and a protective effect of phytoestrogens on breast cancer, but at the present time it is impossible to reconcile dietary/supplement exposure with epidemiological and experimental studies."

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1351–0088/06/013–995 © 2006 Society for Endocrinology *Printed in Great Britain* *Online version via http://www.endocrinology-journals.org*

Exercise and healthy diet

BASIC SCIENCES

Effect of Energy Deficiency on Estrogen Metabolism in Premenopausal Women

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[1]Division of Endocrinology, Metabolism & Diabetes, School of Medicine, University of Colorado at Denver and Health Sciences Center, Denver, CO; and [2]Department of Kinesiology, Noll Laboratory, Pennsylvania State University, University Park, PA

ABSTRACT

WESTERLIND, K. C., and N. I. WILLIAMS. Effect of Energy Deficiency on Estrogen Metabolism in Premenopausal Women. *Med. Sci. Sports Exerc.*, Vol. 39, No. 7, pp. 1090–1097, 2007. **Purpose:** Physical activity has been associated with decreased breast cancer risk, potentially through changes in estrogen metabolism. Two-hydroxyestrone (2-OHE_1) and 16α-hydroxyestrone (16α-OHE_1) have different biological pr
exercise have been fou
to determine whether
2-OHE_1, 16α-OHE_1, o
was 31.6%, and avera
intervention months in
and body weight (3.7 k
and exercise interven
intervention resulted i
did not differ from the
intervention. **Conclusi**
their risk by participat
CALORIE RESTRICT

Westerlind KC & Williams NI. Effect of energy deficiency on estrogen metabolism in premenopausal women, *Med Sci Sports Exer*, Vol. 39, No. 7, pp. 1090-7, July 2007

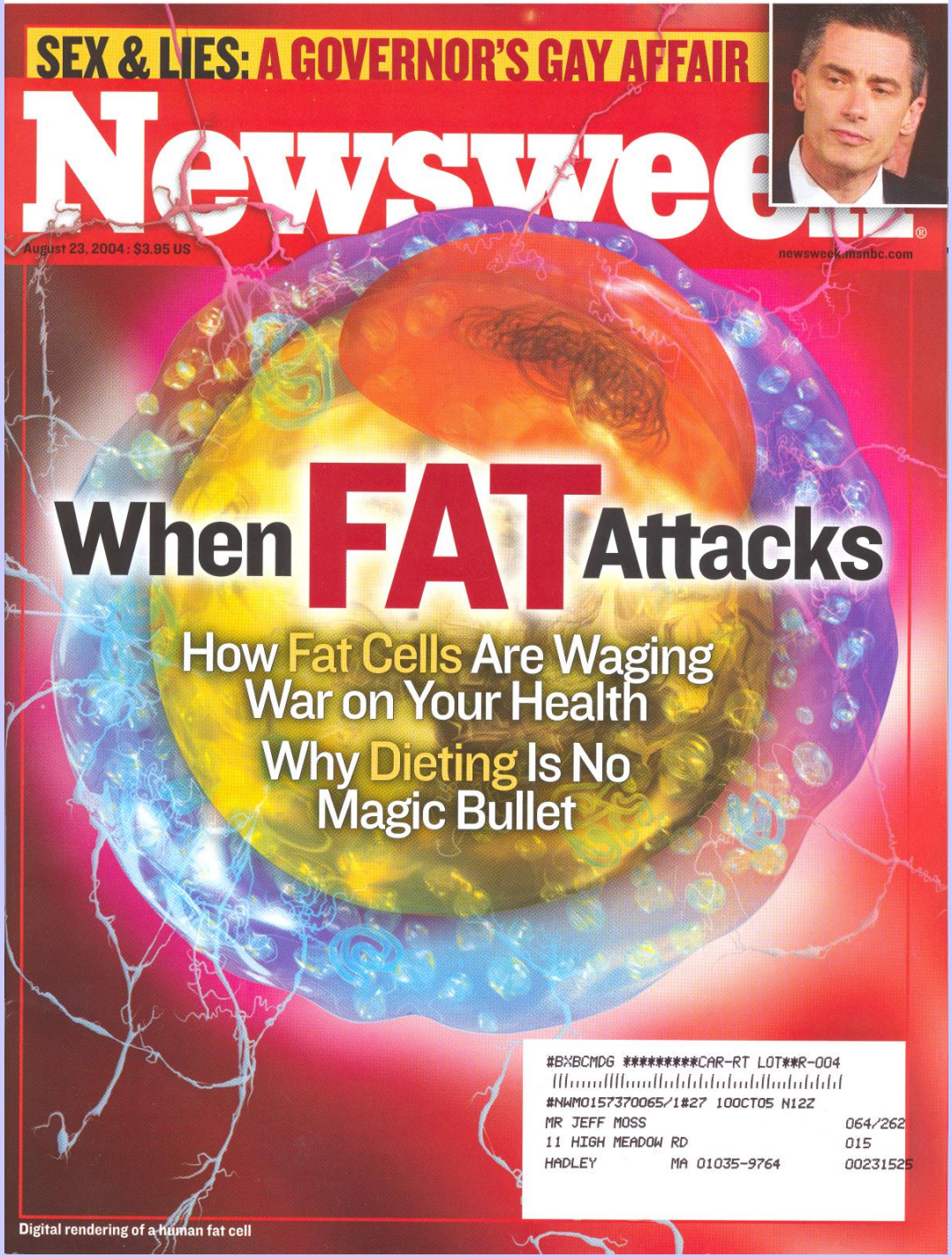
A growing body of
physically active
developing breast
anism for this reduction in risk remains unknown. One biologically plausible hypothesis that has been suggested (18) is that exercise results in lower estrogen levels, and estrogens are strongly implicated in the etiology of breast cancer (14,29). In general, however, the levels of physical activity that have been observed to result in breast cancer risk reduction are unlikely to result in decreases in

such that the energy expenditure of exercise is not matched by increased food intake (8,13). Thus, exercise itself is not viewed as a mechanism to modulate the central control of the reproductive axis (25) and the ovarian output of estrogen.

Given that the levels of physical activity reported to decrease breast cancer risk are unlikely to incur an energy deficit and are, therefore, unlikely to result in decreased

"The data suggest that women at higher risk for developing breast cancer because of low 2/16 may reduce their risk by participating in lifestyle interventions such as exercise/calorie restriction."

Obesity and breast cancer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Breast Cancer Health Center

Obesity Boosts Risk for Aggressive Breast Cancer

Study Shows Link Between Obesity and Triple-Negative Breast Cancer

By Salynn Boyles
WebMD Health News

Reviewed by Laura J. Martin, MD

March 1, 2011 -- Obesity and a sedentary lifestyle appear to increase the risk for an uncommon but aggressive breast cancer that is not fueled by the hormone estrogen, a surprising new study shows.

The analysis of data from a health study involving postmenopausal women revealed that the heaviest women were 35% more likely to develop so-called triple-negative breast cancers than the thinnest women.

Triple-negative breast cancers make up 10% to 20% of all cancers of the breast. They have a poorer prognosis than other tumors, in part because there are no targeted hormonal therapies to treat them.

They are referred to as triple-negative tumors because they do not express the hormones estrogen and progesterone or HER2 protein.

Fat tissue is a significant source of estrogen production in women and obesity is a known risk factor for estrogen-sensitive tumors.

The finding that obesity also appears to raise the risk for triple-negative tumors, which are not fueled by estrogen, was unexpected, study researcher Amanda I. Phipps, PhD, tells WebMD.

Phipps is a postdoctoral fellow at Seattle's Fred Hutchinson Cancer Research Center.

"Hormones are one pathway by which obesity can impact cancer growth, but there are others," Phipps says. "The fact that we see this association with triple-negative tumors suggests that these other pathways are important."

A Visual Guide to Breast Cancer

Exercise, Body Mass Index, and Cancer Risk

The analysis included 155,723 participants enrolled in the Women's Health Initiative (WHI), which followed postmenopausal women for 15 years starting in the early 1990s to assess their risk for cancer, heart disease, and osteoporosis.

During about eight years of follow-up, 307 of the study participants were diagnosed with triple-negative breast cancers and 2,610 were found to have estrogen-sensitive breast cancers.

The women in the study were divided into four groups according to body mass index (BMI).

Compared to women with the lowest BMIs, those with the highest were 39% more likely to be diagnosed with estrogen-sensitive tumors and 35% more likely to have triple-negative tumors.

Compared to women who exercised the least, those who exercised the most were 15% less likely to develop estrogen-sensitive tumors.

The study appears in the March 1 issue of *Cancer Epidemiology, Biomarkers & Prevention.*

African-Americans, Younger Women Have Higher Risk

Triple-negative breast cancers are common among women who have a genetic predisposition known as BRCA1, and they also occur more often in African-American women and tend to occur in younger women.

Body Size, Physical Activity, and Risk of Triple-Negative and Estrogen Receptor–Positive Breast Cancer

Amanda I. Phipps[1], Rowan T. Chlebowski[2], Ross Prentice[1], Anne McTiernan[1], Marcia L. Stefanick[3], Jean Wactawski-Wende[4], Lewis H. Kuller[5], Lucile L. Adams-Campbell[6], Dorothy Lane[7], Mara Vitolins[8], Geoffrey C. Kabat[9], Thomas E. Rohan[9] and Christopher I. Li[1]

+ Author Affiliations

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Amanda I. Phipps, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., M4-B402, P.O. Box 19024, Seattle, WA 98109-1024. Phone: 2066677741; Fax:

Phipps AI et al. Body size, physical activity, and risk of triple-negative and estrogen-receptor positive breast cancer, *Cancer Epidemiol Biomarkers Prev,* Vol. 20, No. 3, pp. 454-63, 2011

Results: Women in the highest versus lowest BMI quartile had 1.35-fold (95% CI, 0.92–1.99) and 1.39-fold (95% CI, 1.22–1.58) increased risks of triple-negative and ER^+ breast cancers, respectively. Waist and hip circumferences were positively associated with risk of ER^+ breast cancer (P_{trend} = 0.01 for both measures) but were not associated with triple-negative breast cancer. Compared with women who reported no recreational physical activity, women in the highest activity tertile had similarly lower risks of triple-negative and ER^+ breast cancers (HR = 0.77; 95% CI, 0.51–1.13; and HR = 0.85; 95% CI,

"Despite biological and clinical differences, triple-negative and ER+ breast cancers are similarly associated with BMI and recreational physical activity in postmenopausal women."

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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Yen SSC. Polycystic ovary syndrome (Hyperandrogenic chronic anovulation), in Yen S et al eds., *Reproductive Endocrinology, 4th Edition*, W.B. Saunders Co., Philadelphia, 1999, pp. 436-478.

"…adipose tissue constitutes a dynamic endocrine metabolic compartment and is influenced by and contributes to the biologic expression of estrogens, androgens, DHEA, glucocorticoids, insulin, and GH-IGFs as well as the production of the hormone leptin."

Yen · Jaffe · Barbieri

Chapter 17

POLYCYSTIC OVARY SYNDROME

Extraovarian Factors (Co-gonadotropins)
Dysregulation of P450c17
Dysregulation of GnRH Pulse Generator
Hereditary and Genetic Factors
LONG-TERM SEQUELAE AND RISKS
Endometrial Cancer

distinct between obese and nonobese women with PCOS.
- GH–IGF-I and insulin are pro-gonadotropins; in synergy with LH, they act on the ovarian theca-stromal cells to stimulate the expression of

- Abnormalities of the reproductive axis are manifested as hypersecretion of LH, theca-stromal cell hyperactivity, and hypofunction of the

by using insulin-sensitizing agents with subsequent amelioration of metabolic and hormonal derangements of the syndrome.

436

International Journal of Obesity (2000) 24, Suppl 2, S1–S3

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Adipose tissue as an endocrine organ

G Ailhaud[1]*

[1]*Laboratoire de Biologie du Développement du Tissu Adipeux, Centre de Biochimie, UNSA, Faculté des Sciences, Nice, France*

The objective is to present a brief overview of peptide and non-peptide factors secreted from adipocytes and to describe some studies on the postulated role of the locally active triad angiotensinogen/angiotensin II/prostacyclin in the development/enlargment of adipose tissue mass and increased blood pressure. In addition to the role of adipose tissue as an endocrine organ, the results emphasize the autocrine/paracrine mechanisms which are postulated to play a role in adipose tissue development and enlargment.
International Journal of Obesity (2000) **24,** Suppl 2, S1–S3

Keywords: angiotensin II; angiote

Ailhaud G. Adipose tissue as an endocrine organ, *Int J Obesity*, Vol. 24, Suppl 2, pp. S1-3, June 2000.

Introduction

The concept that adipose cell
releasing both peptide and no
has emerged over the last dec
allow adipose tissue to com
organs but also allow adipoc
with surrounding cells within t

Secreted proteins and lipid metabolism

Among secreted proteins exhibiting a catalytic activity, lipoprotein lipase has long been known to regulate a critical limiting step at the endothelium cell surface,
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space surrou
regulated by
ASP, which
bined actio
secreted fr
synthesis in

characterization of nuclear receptors of estrogens,[6] androgens[7] and progesterone[8] in human adipose tissue has been reported, which may explain the negative effect of androgens[9] and the positive effect of cortisol[10] on *ob* gene expression and leptin secretion from human adipocytes.

In contrast to androgens and glucocorticoids, estrogens show no effect on both parameters.[9] Together, these results show that adipose tissue is both a

"…adipose tissue is both a producer (and target?) of estrogens and a target of androgens…"

Secreted factors and endocrine functions

That adipocytes are endocrine cells was clearly illustrated by the cloning of the *ob* gene and the subse-

Autocrine/paracrine mechanisms involving secreted factors active in adipose tissue development and enlargment

We reported initially that long-chain fatty acids (saturated and unsaturated) act as transcriptional regulators of lipid-related genes[12] and dramatically enhance the terminal differentiation of preadipose to adipose cells.[13] Among fatty acids, arachidonic acid was characterized as a major adipogenic factor purified from serum[14] and further studies showed that this

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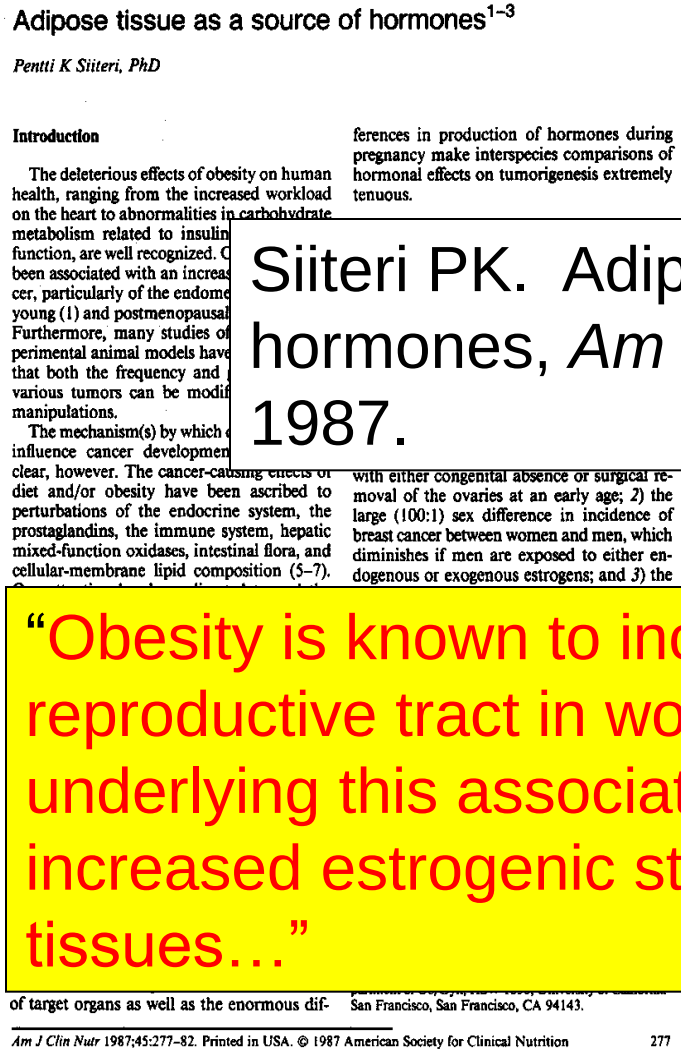


Adipose tissue as a source of hormones[1–3]

Pentti K Siiteri, PhD

Introduction

The deleterious effects of obesity on human health, ranging from the increased workload on the heart to abnormalities in carbohydrate metabolism related to insulin function, are well recognized. C been associated with an increas cer, particularly of the endome young (1) and postmenopausal Furthermore, many studies of perimental animal models have that both the frequency and various tumors can be modif manipulations.

The mechanism(s) by which influence cancer developmen clear, however. The cancer-causing effects of diet and/or obesity have been ascribed to perturbations of the endocrine system, the prostaglandins, the immune system, hepatic mixed-function oxidases, intestinal flora, and cellular-membrane lipid composition (5–7).

of target organs as well as the enormous differences in production of hormones during pregnancy make interspecies comparisons of hormonal effects on tumorigenesis extremely tenuous.

with either congenital absence or surgical removal of the ovaries at an early age; *2*) the large (100:1) sex difference in incidence of breast cancer between women and men, which diminishes if men are exposed to either endogenous or exogenous estrogens; and *3*) the

San Francisco, San Francisco, CA 94143.

Am J Clin Nutr 1987;45:277–82. Printed in USA. © 1987 American Society for Clinical Nutrition

Siiteri PK. Adipose tissue as a source of hormones, *Am J Clin Nutr*, Vol. 45, pp. 277-82, 1987.

"Obesity is known to increase the risk for cancer of the reproductive tract in women. The mechanism underlying this association can be explained by increased estrogenic stimulus to estrogen-target tissues…"

Detoxification and Inflammation

Markers for inflammation discovered in breast cancer survivors are linked to survival

SEATTLE — May 26 — A study led by researchers at Fred Hutchinson Cancer Research Center has identified two proteins in the blood that could become important prognostic markers for long-term survival in breast cancer patients. The proteins are associated with chronic inflammation, which is known to contribute to cancer development and progression.

Cornelia Ulrich, Ph.D., and colleagues measured the levels of C-reactive protein (CRP) and serum amyloid A (SAA) in 734 breast cancer patients at 31 months after diagnosis. They found that elevated levels of CRP and SAA are associated with reduced overall survival, regardless of patient age, tumor stage, race and body mass index. For example, women with breast cancer who had SAA levels that were in the highest third in amount measured in their blood were three times more likely to die from their disease within the following seven years compared to patients with the lowest-third amount. Similarly, women in the highest third of CRP levels had a two-fold increased risk of death.

"These associations are strong and they suggest that, in the long-term, elevated levels of inflammatory markers predict a woman's chances of surviving after breast cancer," said Ulrich, a member in the Hutchinson Center's Cancer Prevention Program. "It also appears that there may be a threshold effect in that only women in the highest third of inflammation markers had increased mortality."

The study appears in the May 18 edition of the Journal of Clinical Oncology.

"To our knowledge, this is the largest population-based cohort study to date that examined the relationship between systemic inflammation and breast cancer survival, and the first to evaluate SAA as a prognostic marker for breast cancer," said Ulrich.

CRP and SAA are nonspecific, acute-phase hepatic proteins that are secreted into the circulating blood stream in response to cytokines including interleukin-1, interleukin-6 and tumor necrosis factor.

Patient data was drawn from the Health, Eating, Activity and Lifestyle (HEAL) study, a multi-ethnic NIH-funded prospective group of women diagnosed with stage 0 through Stage IIIa breast cancer.

In previous studies, elevated CRP was associated with poor survival in patients with metastatic prostate cancer as well as those with gastroesophogeal, colorectal, inoperable small-cell lung and pancreatic cancers. Preoperative levels of SAA have been associated with survival of patients with gastric cancer and those with renal cell carcinoma.

Likewise, clinical and experimental data suggest that chronic inflammation promotes mammary tumor development. Breast cancer patients have elevated concentrations of CRP before surgery, more so in women with advanced disease, which suggests that CRP may be related to tumor burden or progression.

Cancer survivors with chronic inflammation may have an elevated risk of recurrence as a result of the effects of inflammatory processes on cell growth or the presence of cancer cells that induce inflammation, according to the study.

"It is interesting that markers measured in the blood nearly three years after diagnosis predicted prognosis," Ulrich said. "We also found these associations to hold up after adjusting for a number of factors that associate with systemic inflammation, such as obesity. However, more research is needed to confirm these findings and to get more precise estimates of risk. We also need to learn more about the biologic mechanisms."

Ulrich was joined in this study by researchers from the University of Washington, the National Cancer Institute, City of Hope National Medical Center, University of Southern California and the University of Louisville.

Funding for the study was provided by the National Cancer Institute, National Institutes of Health, National Institute of Child Health and Human Development, University of New Mexico, University of Chicago and the California Department of Health.

Note to editors/reporters: For a copy of the paper "Elevated Biomarkers of Inflammation are Associated with Reduced Survival Among Breast Cancer Patients," please contact Kelly Powell, American Society of Clinical Oncology, at 571-483-1365 or Kelly.powell@asco.org)

MEDIA CONTACT
Dean Forbes

Inflammation Is Key to Breast Cancer Growth

View Talk

Submitted by Deborah Mitchell on 2010-12-15 - 13:59

What makes breast cancer develop and grow? Inflammation, say investigators at Kimmel Cancer Center at Thomas Jefferson University. Although inflammation has long been suspected as a culprit in the growth of breast cancer, scientists say this new study proves it.

Selectively stopping inflammation can stop breast cancer

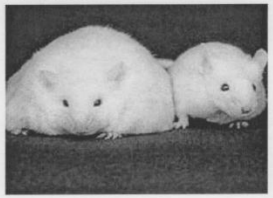
After more than a decade of highly focused research, scientists have proven that an inflammatory process within breast tissue promotes the growth of cancer stem cells that result in tumors. Perhaps even more important is they have shown that when they selectively inactivate the inflammation, they can stop breast cancer from developing.

Scientists have long believed that NFKB (nuclear factor kappa-light-chain-enhancer of activated B cells), which turns on the inflammatory process, is key to the development of breast cancer, but they could not prove it definitively because the mouse models available died when they tried to test their theory.

The development of a new mouse model that allows researchers to regulate the inflammatory system within the adult animal's normal breast tissue made the necessary research possible. Specifically, the researchers found that when they selectively blocked inflammation just in the breast tissue of the new mouse model, tumors did not develop and the number of cancer stem cells also declined.

According to Richard G. Pestell, MD, PhD, director, Kimmel Center and Chairman of Cancer Biology, "these studies show for the first time that inactivating the NFKB inflammatory pathway in the breast epithelium blocks the onset and progression of breast cancer in living animals."

"This finding has clinical implications," says co-author Michael Lisanti, Leader of the Program in Molecular Biology and Genetics of Cancer at



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JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

Chronic Inflammation and Breast Cancer Recurrence

Steven W. Cole, *Division of Hematology-Oncology, Department of Medicine; Jonsson Comprehensive Cancer Center; Norman Cousins Center; AIDS Institute; and Molecular Biology Institute, University of California Los Angeles School of Medicine, Los Angeles, CA*

In this issue of *Journal of Clinical Oncology*, Pierce et al[1] present some of the m
might increase
of 734 women
levels of circula
after treatment
subsequent dis
across primary
and progesterone-receptor status) and independent of potential confounders such as age, estrogen level, and adiposity. These results are consistent with previous studies linking circulating inflammatory markers to progression of metastatic breast cancer.[2-8] However, the findings of Pierce et al are novel in suggesting that serum inflammatory markers might provide early information about disease recurrence risk in patients with no history of metastatic disease and no current evidence of cancer. If the present findings are replicated in larger cohorts with more recurrent cases, post-treatment APP monitoring could provide a new strategy for assessing the risk of breast cancer recurrence in seemingly cured patients.

As the evidence linking chronic inflammation to breast cancer progression grows, it becomes increasingly important to understand why this risk exists and what can be done to ameliorate it. Much research
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report[11] in *JC*
breast cancer i
variation in C
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cardiovascular
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levels of IL-6 c
to *CRP*, upregu
linked to increased risk of breast cancer progression. If the high APP levels observed by Pierce et al[1] emerged solely as a consequence of undetected tumor growth, they might still provide a useful indicator of sub-clinical disease recurrence. However, the existence of cytokine genetic influences on breast cancer progression and links between long-term nonsteroidal anti-inflammatory drug use and reduced breast cancer incidence[16,17] both suggest that the association observed in the study by Pierce et al could have stemmed at least in part from a causal influence of inflammation on breast cancer recurrence. Longitudinal analyses of APP levels in breast cancer survivors would provide additional information regarding the extent to which elevated plasma

associated macrophages, and fibroblasts.[18-21] Systemic inflammation may also condition the vasculature in ways that enhance the extravasation, engraftment, and growth of micrometastases[18,21] or reactivate dormant tumors at distant sites.[22] The emerging role of inflammation in breast cancer progression is remarkable in light of the fact that primary breast tumors rarely in themselves involve significant inflammation. Markedly inflamed breast tumors are uncommon enough to warrant their own diagnostic category.[23,24] However, the biologic processes that drive metastasis or maintain residual disease during therapy may be quite different from those driving primary oncogenesis.[25] Under Paget's analogy,[25] chronic inflammation may fertilize the soil of systemic tissue in ways that promote dissemination and growth of metastatic seeds. Analyses comparing the location and molecular characteristics of primary and recurrent tumors could

untested. It is clear that tamoxifen reduces AI-1 levels, raising the possibility that some protective effects of endocrine therapy might stem from their anti-inflammatory actions. Long-term use of other anti-inflammatory agents such as glucocorticoids, cytokine antagonists, and cyclooxygenase-2 inhibitors is associated with adverse effects that would likely limit their role in adjuvant prevention. Perhaps the most salutary approach would target the upstream factors that drive chronic inflammation, including adiposity and physical inactivity.[9,29] In analyses controlling for age, adiposity, and self-reported physical activity, Pierce et al[1] continued to find that residual variation

Journal of Clinical Oncology, Vol 27, No 21 (July 20), 2009: pp 3418-3419
DOI: 10.1200/JCO.2009.21.8782; published online ahead of print at www.jco.org on May 26, 2009

Cole SW. Chronic inflammation and breast cancer recurrence, *J Clin Oncol*, Vol. 27, No. 21, pp. 3418-9, July 20, 2009.

"Regardless of the specific remedial approach, the present findings…underscore the need to address the broader environment of a patient's global health and behavior as influences on localized neoplastic disease and the resurgence of clinically latent breast cancer."

PalmBeachDailyNews.com
THE SHINY SHEET

Sloan-Kettering researcher discusses inflammation link to breast cancer at Hot Pink symposium

By DAVID ROGERS
DAILY NEWS STAFF WRITER

Updated: 7:30 p.m. Tuesday, Feb. 8, 2011
Posted: 7:20 p.m. Tuesday, Feb. 8, 2011

For a number of years, scientists have known that inflammation plays a role in the progression of coronary artery disease.

Now medical researchers are closer to understanding why inflammation — triggered by an excessive intake of calories — appears to have a hand in the development of breast cancer.

While heredity accounts for 5 percent to 10 percent of cases, most cases of breast cancer are related to environmental factors, including obesity.

That is one of the reasons why breast cancer is more prevalent in affluent, Western societies, according to Dr. Clifford Hudis of Memorial Sloan-Kettering Cancer Center in New York. He is studying the effects of obesity and other factors on the development of breast cancer even after menopause, when natural levels of estrogen decrease in the body. Estrogen can be a fuel for the growth of breast cancer.

Hudis and his co-investigator, Dr. Andrew Dannenberg of Cornell University, are manipulating the diets of laboratory mice, among other steps, to try to understand the development of estrogen-receptive breast cancer in humans.

Part of the investigation is now focused on crown-shaped structures that exist within normal fat cells.

These structures are “very, very inflammatory” and exist in excess in people who are obese, he said.

“And we recently discovered they are present in the breast itself. Why does it matter? It matters because these are little engines of very active chemical production and those chemicals are growth promoters,” Hudis said Monday during a panel discussion at the Breast Cancer Research Foundation’s eighth annual Hot Pink Luncheon and Symposium in Palm Beach.

“What we, of course, are trying to drive ourselves toward is the ability to identify who is really at risk of breast cancer based upon the presence of these structures and, then, of course, ways that we can stop the output of these structures,” said Hudis, chief of breast cancer medicine service at Memorial Sloan-Kettering.

Evelyn Lauder of Palm Beach and New York founded BCRF in 1993 with the sole mission of funding clinical and genetic breast cancer research.

The organization has raised more than $300 million for the cause, she said.

Lauder called Monday’s event, which was held at The Breakers, the most successful the organization has presented in Palm Beach.

According to foundation president Myra Biblowit, the attendance and funds raised at Monday’s luncheon — 232 and $405,000, respectively — set a record for BCRF’s Palm Beach event. — drogers@pbdailynews.com

Find this article at:

http://www.palmbeachdailynews.com/news/sloan-kettering-researcher-discusses-inflammation-link-to-breast-1241462.html

- “For a number of years, scientists have known that inflammation plays a role in the progression of coronary heart disease.”
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- “Part of the investigation is now focused on crown-shaped structures that exist within normal fat cells.”
- “These structures are ‘very, very inflammatory’ and exist in excess in people who are obese, he said.”

NEWS

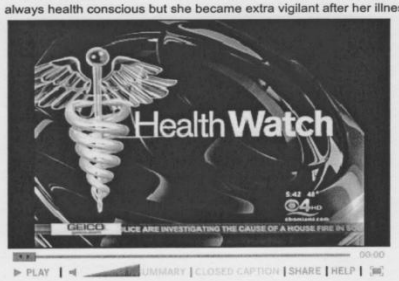
Fish Oil Linked To Lower Breast Cancer Risk

January 14, 2011 10:52 AM

(Photo credit: fisolfishoil.com)

MIAMI (CBS4) — Vitamins and dietary supplements are big business in the U.S. Americans spend about $25 billion a year on supplements including fish oil due to its cardiovascular benefits. But now a new study indicates that the Omega 3 fatty acids found in fish oil may also help women lower their risk of breast cancer.

Sandi Groper is a breast cancer survivor. As a health science teacher she was always health conscious but she became extra vigilant after her illness.



Now she plays golf, watches her weight, goes for yearly mammograms, and takes supplements. Among them are the Omega 3 fish oils.

Fish oil supplements have long been noted for decreasing the risk of cardiovascular disease.

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Current Drug Metabolism, 2001, *2*, 165-183

Hepatic Cytochrome P450 Regulation in Disease States

Po-Yung Cheng and Edward T. Morgan*

Department of Pharmacology, Emory University School of Medicine, Atlanta, GA 30322, USA.

Abstract: Hepatic cytochrome P450 (P450) enzyme activities and gene expression can be profoundly altered in disease states. In general the levels of affected hepatic P450 enzymes are depressed by diseases, causing potential and documented impairment of drug clearance and clinical drug toxicity. However, modulation of P450s is enzyme selective and this selectivity differs among different diseases. This review will concentrate on regulation of P450s in diabetes, obesity and infectious and inflammatory disease, conditions that affect millions of people worldwide every day.

INTRODUCTION AND SCOPE

Individual members of the cytochrome P450 enzyme superfamily are expressed in almo tissue or cell type in the body. The expr activities of the hepatic P450 enzymes ar in a wide variety of disease states, whe regulation of extrahepatic P450 enzymes been so well studied. The hepatic cyto P450 of the families CYP1-4 have the m in drug clearance, and thereby determ response to a given drug dose or Therefore, this review will concentrate regulation of the hepatic drug-metabolizing P450 enzymes in disease.

Much more is known about the effects of disease on drug metabolism in animals than in humans. Studies in humans generally have been limited to studying drug clearance or in vivo metabolite ratios, and it is important to note that, as reviewed by McKindley *et al* [1], hepatic drug clearance is affected not only by the enzymatic activity in the liver, but also by hepatic blood flow and plasma protein binding. Hepatic clearance of drugs with a high intrinsic clearance (e.g. propranolol) is mainly limited by blood flow, and therefore changes in hepatic P450 enzyme levels may not result in a change of corresponding magnitude in the clearance of such drugs. In contrast the hepatic clearance of drugs with a low or intermediate intrinsic clearance (e.g. mida-

observed in this disease state.

DIABETES AND OBESITY

Diabetes mellitus is a group of metabolic diseases, whose common feature is hyperglycemia caused by defective insulin secretion, or by a defective tissue response to insulin. It afflicts approximately 3% of the world's population: in 1997, 10.3 million Americans were diabetics and it has been estimated that almost the same number have undiagnosed diabetes [2]. Two types of diabetes predominate in the population. Type 1 diabetes is a disease of insulin deficiency comprising about 10% of all cases of diabetes, and is characterized by the autoimmune destruction of the pancreatic β cells [3]. It is often juvenile in onset and is treated with insulin.

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1389-2002/01 $28.00+.00

Cheng PY & Morgan ET. Hepatic cytochrome P450 regulation in disease states, *Curr Drug Metab*, Vol. 2, pp. 165-183, 2001

Table 2. Cytokine Regulation of P450 Expression in Human Hepatocytes

P450	Inducer	Cytokine	Effect	Reference
1A1	3-MC[a], 3-methylcholanthren	TGFβ	↓	[116]
	BNF	IL6, TNFα,	↓	[86]
1A2	none	Oncostatin M, IL6, IFNγ, TNFα, TGFβ,	↓	[116,133,134]
	3-MC	Oncostatin M, TGFβ, IFNγ,	↓	[99,116,133]
	BNF	IL6, TNFα,	↓	[86]
2A6	none	Oncostatin M, IL6, IFNγ,	↓	[133]
	3-MC	IFNγ	↓	[99]
2B6	none	Oncostatin M, IL6, IFNγ,	↓	[133]
	3-MC	IFNγ	↓	[99]
2C	none	TNFα	↓	[134]
2E1	none	IL1,IL6,TNFα, IFNγ,	↓	[134]
	none	IL4	↑	[134]
3A4	none	IFNγ, Oncostatin M, IL1,IL6,TNFα,	↓	[99] [133,134]
	none	IFNγ	→	[134]
	3-MC	IFNγ	↓	[99]
	dexamethasone	Oncostatin M,	↓	[133]
	rifampicin	IL6	↓	[86]
	rifampicin	IL1, TNFα	→	[86]

Current Drug Metabolism, 2004, *5*, 235-243

Cytochrome P450 Regulation and Drug Biotransformation During Inflammation and Infection

Kenneth W. Renton*

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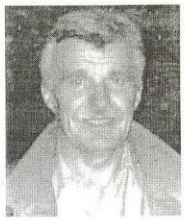

Abstract: The expression of cytochrome P450 and related biotransformation is altered during the operation of host defense mechanisms. This has major implications in inflammation and infection when the capacity of the liver and other organs to handle drugs is severely compromised. In most cases individual cytochrome P450 forms are down regulated at the level of gene transcription with a resulting decrease in the corresponding mRNA, protein and enzyme activity. The loss in drug metabolism is channeled predominantly through the production of cytokines which ultimately modify specific transcription factors. Other proposed mechanisms that apply to specific cytochrome P450s involve post translational steps including enzyme modification and increased degradation. When inflammatory responses are confined to the brain there is a loss of cytochrome P450 not only in the brain but also in peripheral tissues. This involves a yet to be identified mode of signaling between the brain and periphery but it does involve the production of cytokines from a peripheral source. In clinical medicine there are numerous examples of a decreased capacity to handle drugs during infections and disease states that involve an inflammatory component. This often results in altered drug responses and increased toxicities. Inflammation mediated alterations in the metabolism of endogenous compounds can lead to altered physiology. Changes in drug handling capacity during inflammation/infection will continue to be one of the many factors that complicate therapeutics.

1. INTRODUCTION

Since the cytochrome P450 family of enzymes is critical to the metabolism and subsequent excretion number of therapeutically used drugs, it is not sur factors that evoke changes in individual forms of have a significant influence on successful therapy it was first observed over 25 years ago, it is or that the practical importance of changes to cytoch during the activation of host defense mechanism recognized as playing a role in the activation or of some key drugs. Infection and inflammatory are commonplace and any concomitant chang disposition during such disease states likely contr overall inter-individual variability in drug response and toxicity. Changes caused by inflammatory responses are superimposed on the alterations to this enzyme system caused by a variety of other factors. In addition to changes in drug disposition several of the cytochrome P450s that are involved in the biotransformation of endogenous chemicals are also changed in infection and inflammation and this leads to an alteration in the corresponding physiological function. The reason why responses to infection or inflammation include a change in the capacity to metabolize drugs and chemicals has been subject to much speculation [1, 2]. It is however ironic that the system that has likely evolved to protect us against living organisms has the ability to interfere with the system that has evolved to protect us against chemical entities. In this review recent information on inflammation/infection evoked changes in cytochrome P450 mediated drug and chemical metabolism is discussed and an attempt is made to show the relevance of these changes in

although there are a few exceptions in which the inflammatory response increased a cytochrome P450 form. The effects of lower cytochrome P450 levels have been reported widely and result in lowered drug clearance, increased toxicity and altered physiology in the case of endogenous chemicals [1-4]. The consequences of enhanced cytochrome P450 during infection can also be profound as illustrated by Serrano *et al.* who demonstrated that CYP1A1 and CYP2B1 were increased in rats during infections with *Taenia taeniformis* [5]. This resulted in the formation of significant genotoxic damage when benzo(a)pyrene, cyclophosphamide or aflotoxin B(1) were administered during the period of enhanced metabolism. Infectious agents known to alter cytochrome P450 forms are listed in Table **1**.

Inflammation

Responses to inflammation are a complex response to tissue damage, infection, burns, trauma, tumors and autoimmune disease. A large number of articles have now been

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1389-2002/04 $45.00+.00

Renton KW. Cytochrome P450 regulation and drug biotransformation during inflammation and infection, *Curr Drug Metab*, Vol. 5, No. 3, pp. 235-43, June 2004

Table 1. Infectious Organisms that Modulate Cytochrome P450 Dependent Drug Biotransformation

	INFECTIOUS AGENT	SPECIES
Virus	Mouse Hepatitis virus	Mouse, Duck
	Hepatitis A	human
	Encephalomyocarditis virus	rat
	Mengo virus	rat
	Newcastle Disease Virus	mouse
	Influenza A and B	human, mouse
	Cytomegalovirus	mouse
	Retrovirus (LP-BM5)	mouse
	Adenovirus	human
	Herpes simplex	human
	HIV	human
	Coxackievirus B3	mouse
Bacteria	*Listeria monocytogenes*	mouse, fish
	Chlamydia trachomitis	mouse
	Actinobacillus pleuropneumonia	pig
	Helicobacter hepaticus	mouse
	Helicobacter pylori	human
	Opisthorchiasis viverrini	human
Parasitic	*Fasciola hepatica*	mouse, rat, sheep
	Plasmodium berghei	mouse, rat
	Plasmodium falciparum	human
	Schistosoma mansoni	rat, mouse, human
	Toxoplasma gondii	mouse
	Taenia crassiceps	mouse
	Taenia taeniformis	rat

Table 2. Inflammatory and Immuno-Stimulating Agents that Depress Cytochrome P450 Dependent Drug Biotransformation

Trypan Blue	Zymosan
Dextran sulphate	Latex breads
Turpentine	Carrageenan
Adjuvants	Barium sulphate particulate
Particulate irritants	Vaccines
Tissue Injury	Surgical stress
Tumors	Autoimmune encephalomyelitis
Interferon inducers	Poly rI.poly rC
Interferons α, ß and γ	Interleukin -1α, -1ß, -2, and -6
Transforming growth factor ß	TNF-α
E. coli lippolysaccharide (LPS)	*Corynobacterium parvum*
Staphylococcal enterotoxin B	*Staphylococcal aureus* protein A
Kelbsiella pneumoniae endotoxin	*Bordetella Pertussis* toxin

Causes of chronic inflammation

- Nutrient deficiency, excess or imbalance
- Food allergy or intolerance
- Infection
- Lack of sleep
- Toxins
- Stress responses and effects
- Trauma
- Excess body fat
- Balanced and coordinated movement against gravity
- Bad thoughts
- Lack of optimal sunshine
- Suboptimal use of supplements
- Suboptimal relationships
- Oxidation

Some parting thoughts