Clinical application of DUTCH test in a woman diagnosed with breast cancer

18th July 2024

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ICT FELLOWSHIP

PRACTITIONER METABOLIC APPROACH TO CANCER GRADUATE dr nasha MTIH.ORG

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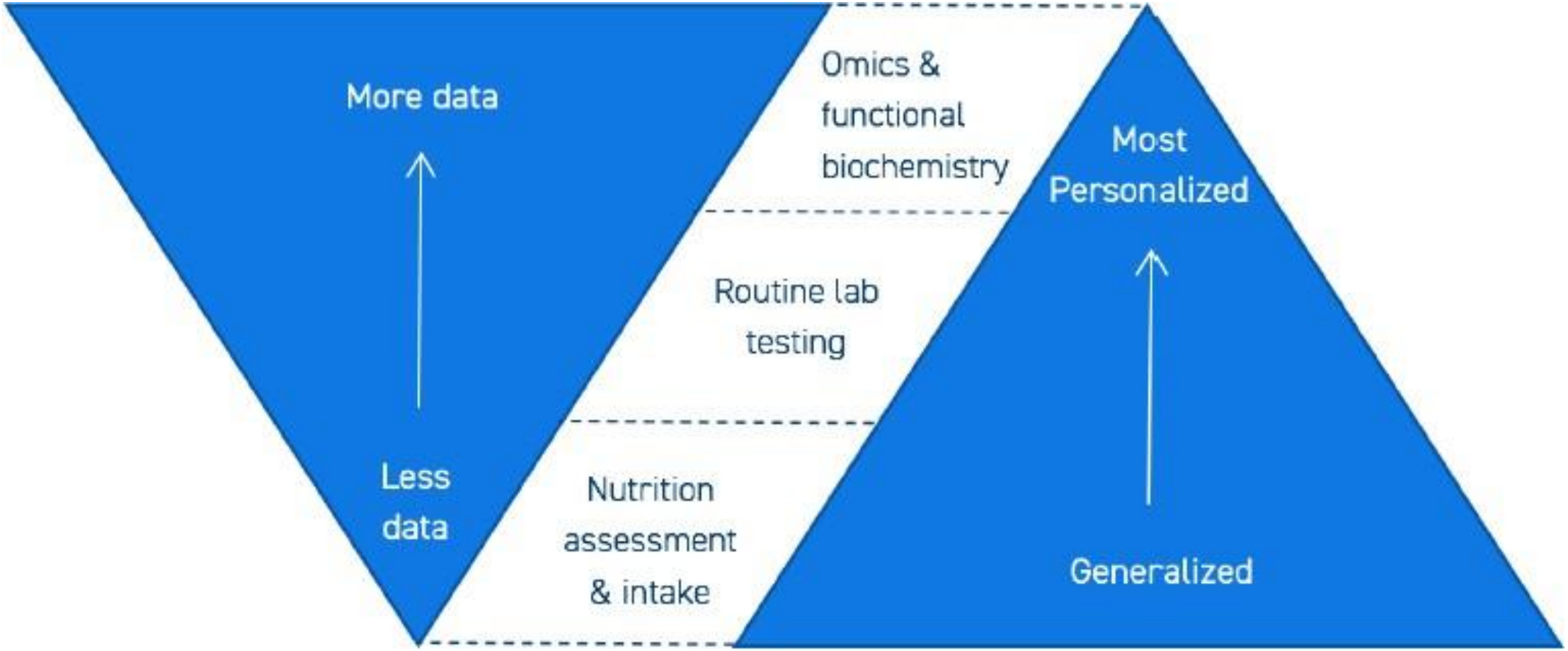
Embracing Nutrition & Functional Medicine


LET'S
GO.

Personalized Nutrition: Interactions Between Data and Outcome



Meet Jayne

- A 48 year old female with a diagnosis of triple positive breast cancer with nodal involvement to the left breast.
- Whilst Jayne had shown intuition to her own wellness and self-compassion for years she had lost touch with this in the period immediately before diagnosis and had started smoking again (having not for 10 years)
- Diagnosed June 2021 after finding a lump in her breast
- A biopsy, ultrasound and mammogram confirmed the diagnosis
- Treatment already completed:
    - Paclitaxol weekly for 12 weeks
    - Phesgo 3 weekly
    - Then surgery
    - Kadcyla 14 cycles
    - Radiation: 15 sessions
    - Anastrazole (now took self off) and periods have returned

Other significant considerations

- Vegan diet
- Runs low on iron
- Stress a huge trigger and whilst lots of work has been done on this: anxiety is still a factor
- ACEs as a child
- 1 seven year old child who was breast fed for 4 years
- No previous significant medical history
- Diarrhea through treatment which is still ongoing
- No family history of cancer
- Diagnosis of osteopenia since treatment
- COVID mid treatment which triggered loss of smell
- BMI: 19 (dropped to 17 during treatment)
- Liver enzymes still elevated post treatment
- Has historically done a lot of yoga but currently swimming

Plan 1

Focus on diversity for the gut (vital for oestrogen excretion)
Broccoli sprouts (client happy to sprout)
Liver supporting foods and herbal teas
Time restricted eating

Sleep hygiene
Load bearing exercise
EMF exposure

DUTCH as stopped anastrazole
Lifecode genomics: hormones and detoxification

Steroid Pathways

Find these Hormones on the DUTCH Report

www.dutchtest.com

Primary hormones (in CAPS) are made by organs by taking up cholesterol ★ and converting it locally to, for example, progesterone. Much less is made from circulating precursors like pregnenolone. For example, taking DHEA can create testosterone and estrogen, but far less than is made by the testes or ovaries, respectively.

★ → Pregnenolone

Ketoconazole[29], spironolactone[30], apigenin, polyphenols[31, 32] (−)

Pregnenolone —17-hydroxylase→ 17-OH-Pregnenolone —17,20 Lyase→ DHEA

Licorice root[34, 35], spironolactone[37], azole antifungals[38], hyperglycemia[27], apegenin[31, 38] (−)

Hyperglycemia[27], hyperinsulinemia[28] (+)

PCBs[33], DHEA supplements[7], obesity[36] (+)

DHEAS (Sulfate)

Where is it made? Adrenal gland

Spironolactone[84], dexamethasone[85], bile acid[86], St. John's Wort[84], forskolin[87] (+)

Low cysteine[88], inflammation[88], LPS[89], ketoconazole[88], progestin[83], licorice[90] (−)

DHEA —17βHSD→ Androstenediol

Isoflavonoids/phytoestrogens[4], phthalates, organochlorines, BPA[5], ketoconazole[5], finasteride, dutasteride (−)

Fenugreek[1], high ACTH/hyperadrenalism[2], PCOS[3] (+)

Where is it made? Ovaries – less from adrenals

3βHSD

PROGESTERONE —17-hydroxylase→ 17-OH-Progesterone —17,20 Lyase→ Androstenedione

Androstenediol —3βHSD→ TESTOSTERONE

Where is it made? Testes in men, from the ovaries and adrenal DHEA in women.

Enterolactone, apigenin, genistein, chrysin and other flavonoids[52], white button mushrooms[53], grape seed extract, red wine procyanidin dimers[55], PCOS[56], antifungal medications[57], metformin[58] glyphosate[59], aromatase inhibitors (letrozole, anastrozole) (−)

PROGESTERONE —5α→ a- Pregnanediol

PROGESTERONE —5β→ β- Pregnanediol

Androstenedione —5β→ Etiocholanolone

Androstenedione —Aromatase (CYP19), 5α→ Epi-Testosterone

Androstenedione —CYP21→ 17-OH-Progesterone —CYP11b1→ CORTISOL (active)

Where is it made? Adrenal gland

More Cortisone: EGCG[20], PCOS[3], curcumin[21], 7-keto-DHEA[19], progesterone[19], coffee[22], holy basil[22], bitter melon[24], hyperthyroidism[19, 26], high estrogens[19], glucocorticoids[19]

CORTISOL (active) —11β-HSD→ Cortisone (inactive)

More Cortisol: Insulin resistance, obesity[6, 17], inflammation[18], hypothyroidism[25], licorice root[19], phthalates, organotins, alkylphenols[19], mother's diet during pregnancy[19]

TESTOSTERONE —5α→ 5α-DHT —3αHSD→ 5α-Androstanediol

Obesity and inflammation[46], high insulin[47], forskolin[48], quercetin, genistein (bioflavonoids)[49], white peony and licorice root[50], atrazine[51], rutin[59] (+)

Etiocholanolone —3αHSD→ 5β-Androstanediol

Androsterone —17βHSD→ 5α-Androstanediol

Rutin[39], alcohol[41], abdominal obesity[42], bioflavonoids[43] (+)

Licorice[4, 34, 35], apigenin[4,38], pyhtoestrogens[4, 40], atrazine[45] (−)

TESTOSTERONE —Aromatase (CYP19)→ ESTRADIOL (E2)

Where is it made? Ovaries – lesser amounts elsewhere from DHEA/ Testosterone.

Estrone (E1) —17βHSD→ ESTRADIOL (E2)

St. John's Wort[74], pesticides[75], caffeine[62], smoking[62], PAHs[74], moderate alcohol consumption[68], obesity[68] (+)

Grapefruit[60], resveratrol[60], rosemary[65], wild yam[77], peppermint oil[78], azole antifungals[79] (−)

Estrone (E1) —CYP-3A4*→ 16-OHE 1 —17βHSD→ Estriol (E3)

ESTRADIOL (E2) —3A4*→ Estriol (E3)

Flavonoids[73], resveratrol[71] (−)

Inflammation[70], smoking[71], PAHs[69] (+)

Estrone (E1) —CYP-1A1→ 4-OHE1 —COMT→ 4-MeOE1

Cruciferous vegetables[60], DIM/I3C[61], caffeine[62], soy[63], fish oil[64], rosemary extract[65], thyroxine[66], flaxseed[67] (+)

Estradiol[80], phthalate esters[81], rhodiola rosea, quercetin, catechin and epicatechin[82]

Estrone (E1) —CYP-1B1→

α-THF

THF

THE

*5α-Reductase/5β-Reductase

5α-Reductase is best known because it makes androgens like testosterone more potent. It is also responsible for metabolizing progesterone and cortisol. If up-regulated, it may cause high androgen symptoms in men (thinning hair, prostate) and women (as in PCOS, thinning hair, acne, facial hair growth). 5β-Metabolites are less androgenic (weaker).

5α-Reductase is increased in particular by: Insulin resistance and obesity[6], DHEA supplementation[7], PCOS[8]

5α-Reductase may be decreased by: Saw palmetto and beta-sitosterol[9], reishi[10], nettle root[11], Pygeum africanum[12], PUFA and EGCG[13]

5β-Reductase may be affected by some of the above listed things as well (often to a lesser degree).

5β-Reductase may be increased by: Insulin resistance, high triglycerides[14], PCOS[15]

5β-Reductase may be decreased by: Licorice[16]

Cortisol Metabolism/Clearance

Cortisol is metabolized by 5α/5β-reductase (and 3α-HSD) to α/β-THF & THE for excretion. This process is particularly increased in obesity, high insulin and hyperthyroid. It may be slowed in cases of hypothyroidism, anorexia,

*CYP3A4

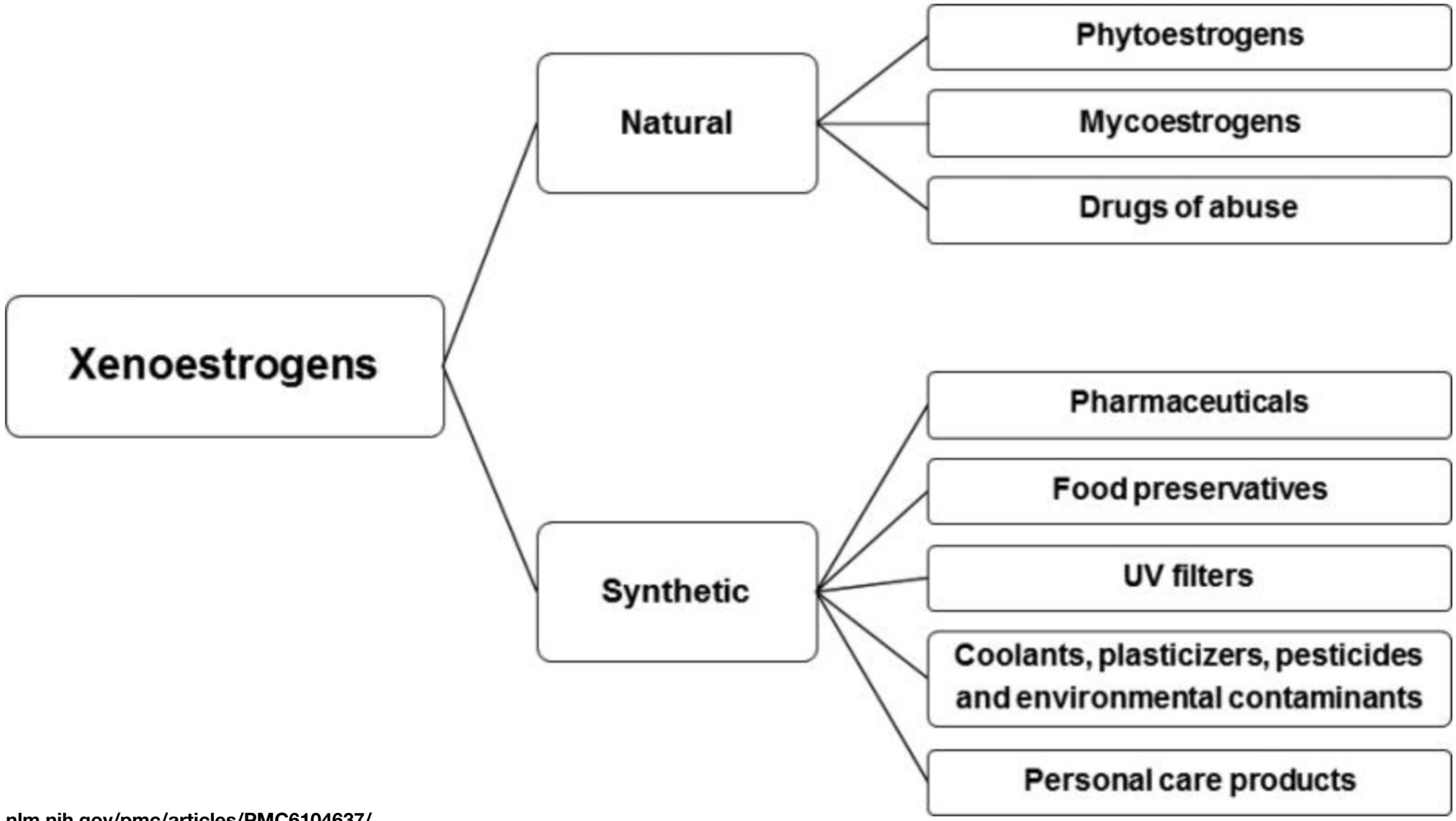
Many common medications induce CYP3A4, including but not limited to, phenobarbitol, phenytoin, rifampicin, and glucocorticoids.

Common medications interfere with or competitively inhibit CYP3A4 including cimetidine, tamoxifen, quinolones, fluoxetine, etc...

“Epidemiological data strongly suggest that a woman's risk of developing breast cancer is directly related to her lifetime estrogen exposure. Estrogen replacement therapy in particular has been correlated with an increased cancer risk.”

Zhang F, et al. Equine estrogen metabolite 4-hydroxyequilenin induces DNA damage in the rat mammary tissues: formation of single-strand breaks, apurinic sites, stable adducts, and oxidized bases. Chem Res Toxicol. 2001;14(12):1654-9.

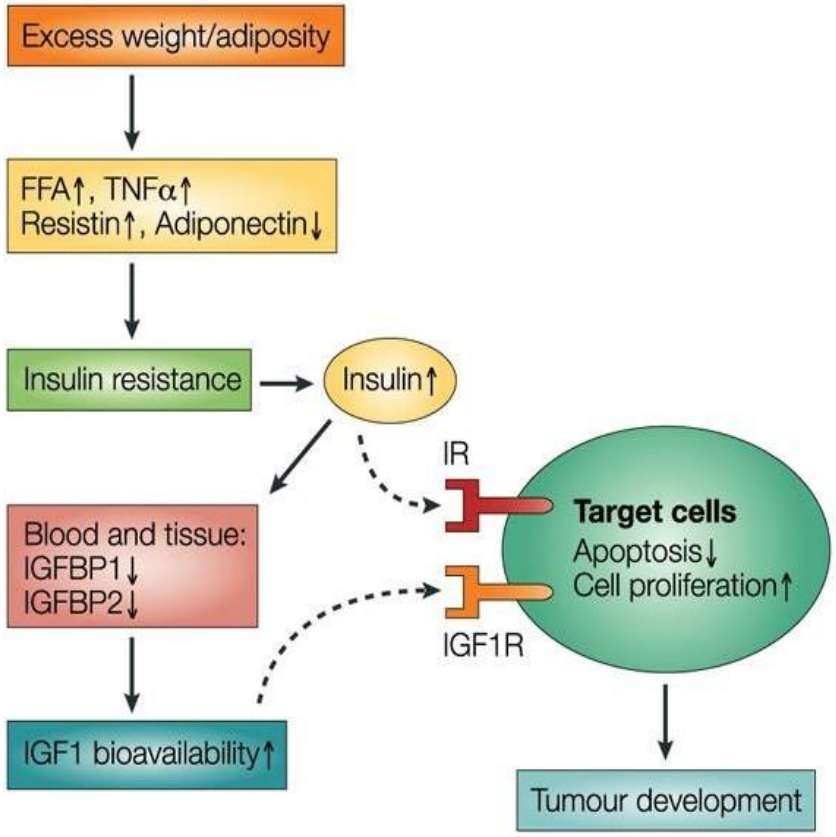
Classification of xenoestrogens



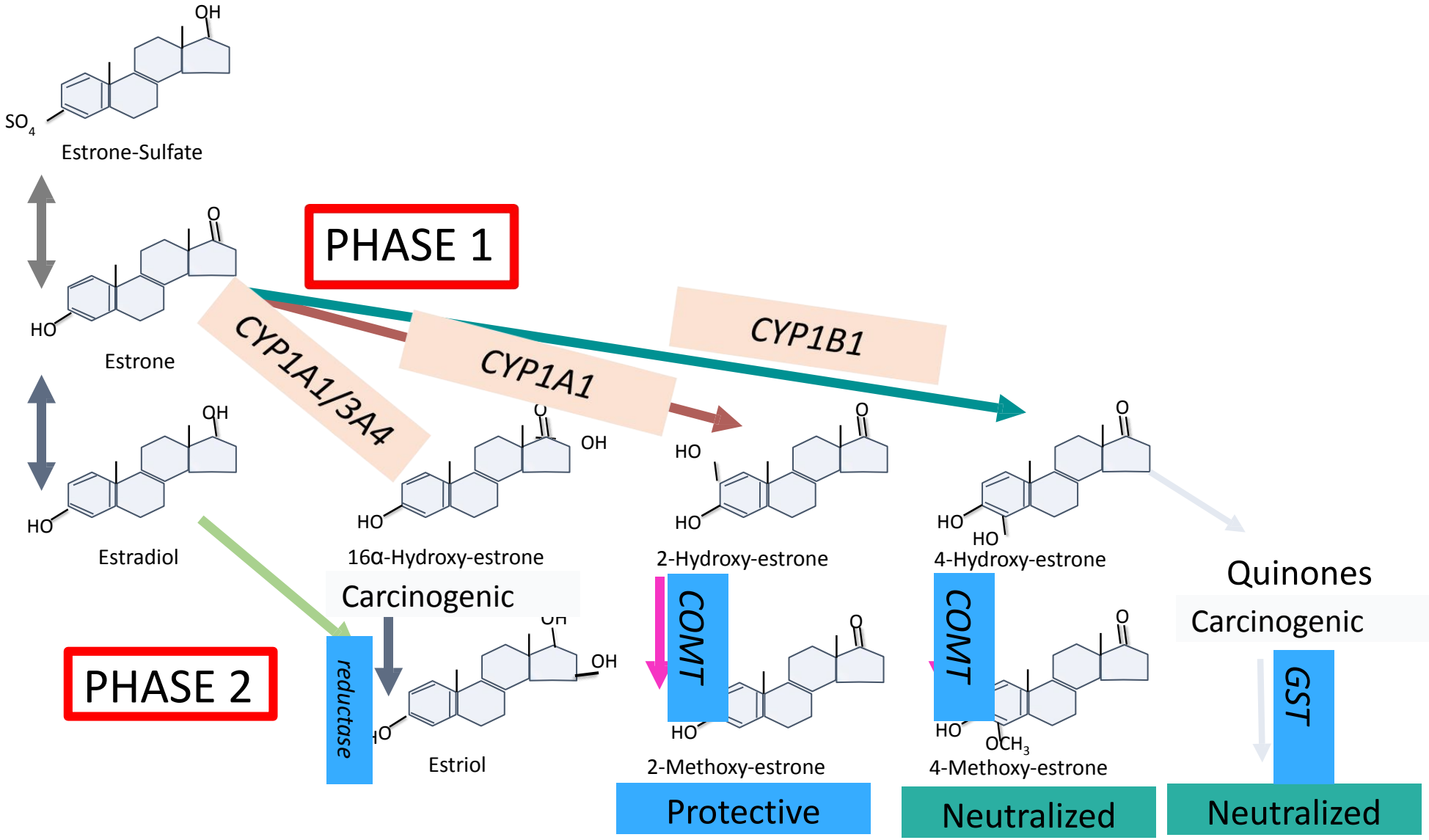
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6104637/

Insulin Resistance- fuels the E2 factory in breast

- Mitogenic
- Anti-apoptotic
- Proangiogenic
- Increases IGF-1
- Pro-inflammatory



Sub-optimal Hormone Metabolism



Clinics (Sao Paulo). 2021; 76: e2846.
Published online 2021 Jun 7. doi: 10.6061/clinics/2021/e2846
PMCID: PMC8183338
PMID: 34133482

Influence of *CYP19A1* gene expression levels in women with breast cancer: a systematic review of the literature

Maria da Conceição Barros-Oliveira,[I] Danylo Rafhael Costa-Silva,[I] Alesse Ribeiro dos Santos,[II] Renato Oliveira Pereira,[I] José Maria Soares-Júnior,[III] and Benedito Borges da Silva[I,II,*]

Author information ▸ Article notes ▸ Copyright and License information PMC Disclaimer

Abstract

Go to:

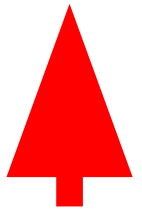
Breast cancer is the most frequently diagnosed malignant neoplasm in women and is considered a multifactorial disease of unknown etiology. One of the major risk factors is genetic alteration. Changes in *CYP19A1* gene expression levels have been associated with increased risk and increased aggressiveness of breast cancer. Increased *CYP19A1* gene expression and/or aromatase activity are among the major regulatory events for intratumoral production of estrogens in breast malignant tissues. This systematic review aimed to investigate the influence of *CYP19A1* gene expression levels in women with breast cancer. The research was carried out using the PubMed, Scopus, and Web of Science databases. Searches were conducted between February 2 and May 15, 2019. Inclusion criteria were studies published between 2009 and 2019, English language publications, and human studies addressing the gene expression of *CYP19A1* in breast cancer.

A total of 6.068 studies were identified through PubMed (n=773), Scopus (n=2,927), and the Web of Science (n=2,368). After selecting and applying the inclusion and exclusion criteria, six articles were included in this systematic review

CYP19A1
Codes for Aromatase

SNP - higher activity
More Oestrogen

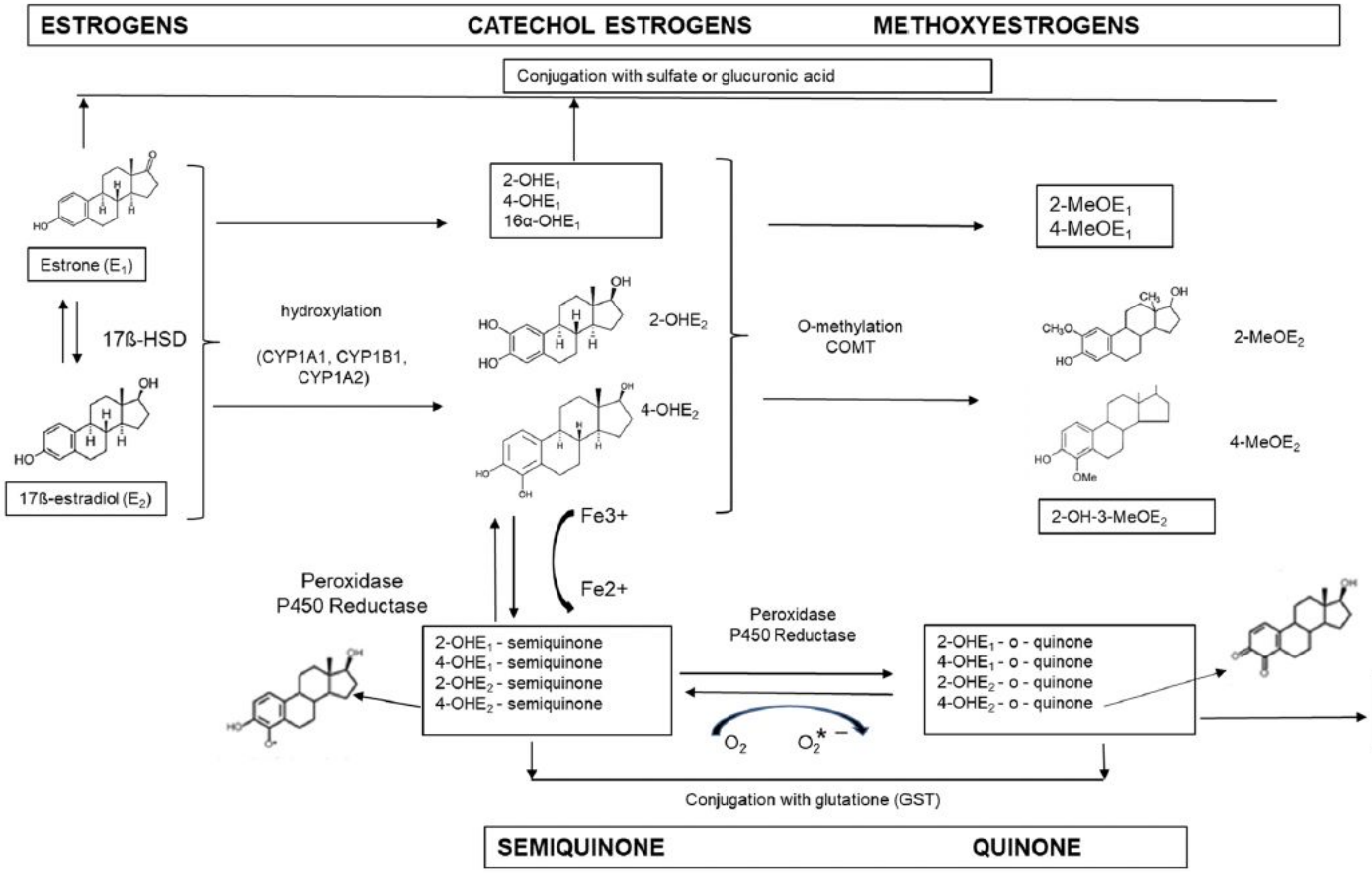
Insulin resistance, Obesity (adipose tissue), Cortisol (stress), Testosterone (and anabolic steroids), **Alcohol**, Inflammation, Age



Flavonoids, Zinc, Resveratrol, Green Tea, DIM, Mustard Greens, Broccoli, Olive Oil, Vitamin E, Celery, White Button Mushrooms

Aromatase inhibitor medications - anastrozole, letrozole (in gender transition (F-M) and breast cancer treatment).

Hydroxylation



https://link.springer.com/article/10.1007/s43440-021-00317-0

CYP1B1

Hydroxylation

SNP - higher activity

ore OH-Oestrogens

H. Stress. Inflammation

CG, Olive Oil, broccoli extract

QO1

uinone Dehydrogenase

NP - lowers activity (more risk of idative stress, cancer)

ılphoraphane - in mustard, cabbage, orseradish, induces NQO1. B2 is cofactor

STM1/P1

Conjugate Semi-quinones

Glutathione

Volume 63, Issue 23
1 December 2003

Previous Article Next Article

Article Contents

ENDOCRINOLOGY | DECEMBER 16 2003

Sequential Action of Phase I and II Enzymes Cytochrome P450 1B1 and Glutathione S-Transferase P1 in Mammary Estrogen Metabolism FREE

David L. Hachey;

Check for

+ Author & Articl

Cancer Res (200

Article histor

Split-S

Abstract

The Phase I
estrogen-indu
(E_2) to catecl
and E_2-3,4-Q
decreased by
glutathione S
and Phase II
and GSTP1 t

Original Article | Published: 28 April 2017

Glutathione S-transferases deletions may act as prognosis and therapeutic markers in breast cancer

Clodoaldo Zago Campos, Roberta Losi Guemb
Banin Hirata, Glauco Akelinghton Freire Vitiello
Ehara Watanabe & Tânia Longo Mazzuco

Clinical and Experimental Medicine **18**, 27–35

433 Accesses | **12** Citations | Metrics

Abstract

Breast cancer (BC) is the main worldwide
xenobiotic absorption and elimination rat
damage and, consequently, tumor develop
as GSTM1 and GSTT1, and the NAD(P)H
involved in phase II detoxification reactio
nucleotide polymorphism (SNP) in *NQO1*

Analyses of bulky DNA adduct levels in human breast tissue and genetic polymorphisms of cytochromes P450 (CYPs), myeloperoxidase (MPO), quinone oxidoreductase (NQO1), and glutathione *S*-transferases (GSTs)

Ulrike Brockstedt [a], Maja Krajinovic [a], Chantal Richer [a], Geraldine Mathonnet [a], Daniel Sinnett [a], Wolfgang Pfau [b], Damian Labuda [a]

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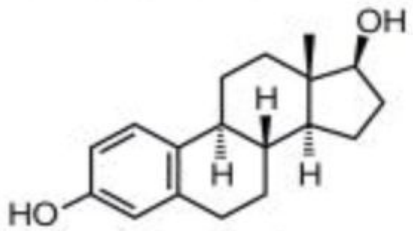
https://doi.org/10.1016/S1383-5718(02)00019-0 Get rights and content

Abstract

Environmental carcinogens are converted into DNA-reactive metabolites by phase I and phase II enzymes that are involved in the activation and detoxification of xenobiotics. Several of these enzymes display genetic polymorphisms that alter their activity leading to individual variation in DNA damage levels and thus cancer susceptibility. We investigated the relationship between DNA adduct levels and genetic polymorphisms in key enzymes of chemical carcinogenesis: CYP1A1,

Estradiol



P450s e.g. 1B1

Catechols

e.g. 4-OHE2

e.g. 4-OHE2

Estrogenic

Quinones

ROS
DNA Damage
Carcinogenic

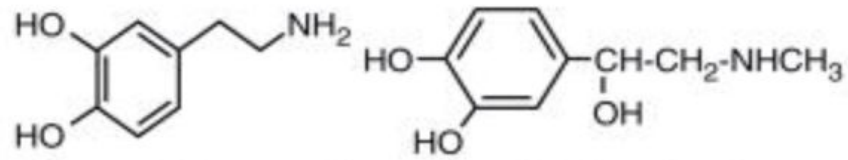
COMT

Active O-methylated
Metabolites
e.g. 2-Me E2: Anticarcinogenic;
Cardioprotective

Inactive O-methylated
Neurotransmitter
and Catechol Metabolites

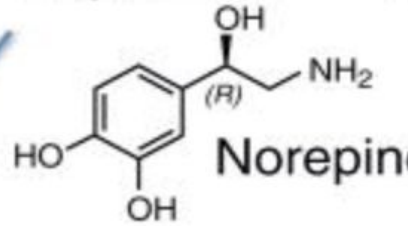
Neurotransmitters - catecholamines

Ex:



Dopamine

Epinehprine



Norepinehprine

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3665426/

Methylation

- Unlocks our bodies healing response
- Responsible for billions of processes every moment
- All based on methyl groups
- Prevention/driver of every chronic issue

Functional roles of methylation

- Gene regulation (activation/inactivation)
- Biotransformation (phase 2)
- Neurotransmitter formation: dopamine, adrenaline and serotonin
- Hormone biotransformation- Estrogens
- Immune cell differentiation (T cells, NK cells)
- Energy metabolism (CoQ10, carnitine, ATP)
- Myelination of peripheral nerves
- RNA and DNA synthesis
- Post-transcriptional modulation (eg Methylcytosine)

Quinones

- Quinones are thought to play a role in carcinogenesis by inducing DNA damage directly or as a result of redox cycling.
- Supplementation with antioxidant nutrients can reduce the oxidation of the catechols and promote greater excretion of these metabolites through the methylation pathway.

Bolton JL, Pisha E, Zhang F, et al. Role of quinoids in estrogen carcinogenesis. Chem Res Toxicol 1998;11:1113-27.

Quinones

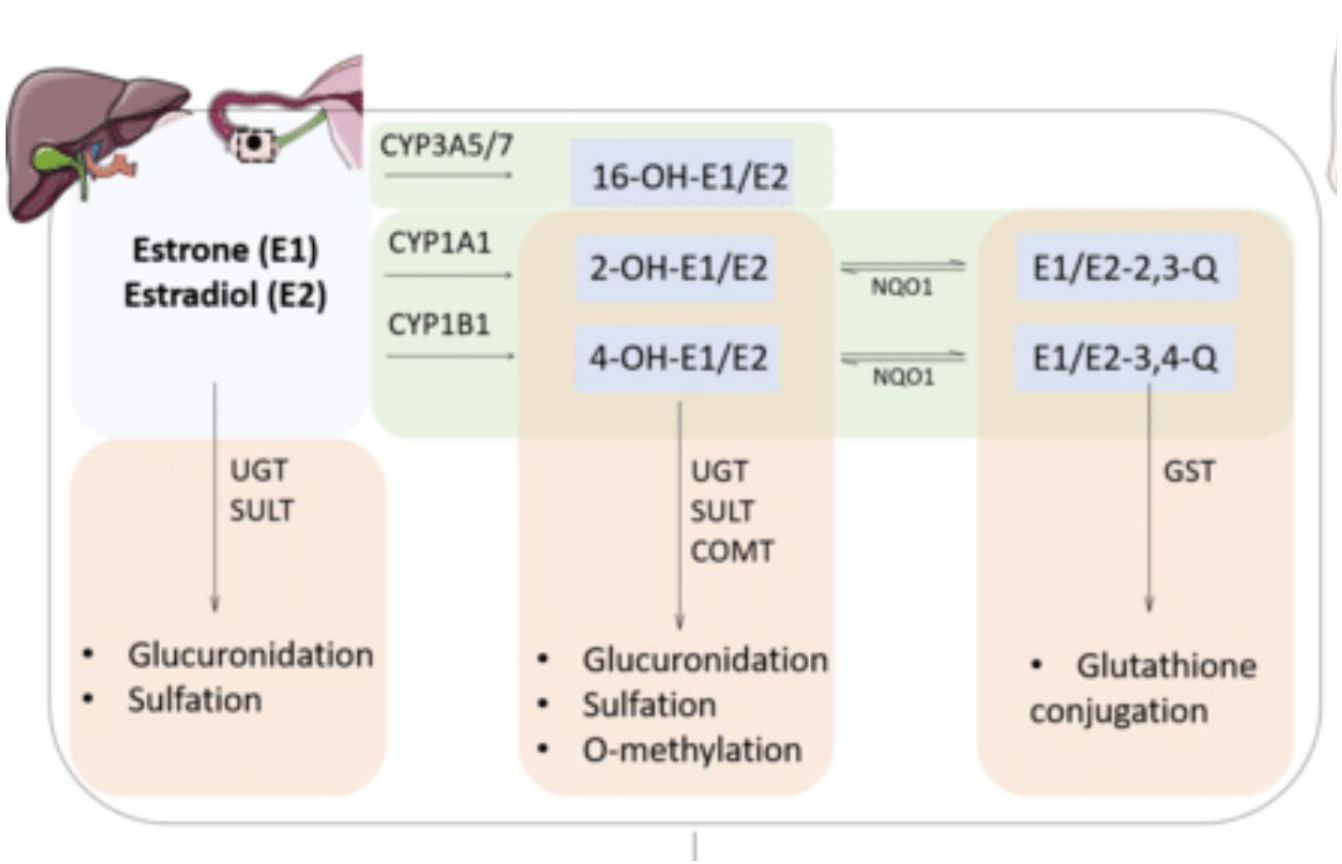
- Formed if methylation does not take place
- Highly reactive
- Damage DNA and promote carcinogenesis
  - Directly
  - Indirectly through the production of free radicals
- Can be “deactivated” by glutathione-S-transferase to produce a mercaptopurate.

Chronic restraint stress massively alters the expression of genes important for lipid metabolism and detoxification in liver

>235 genes were up- or down-regulated by >1.8-fold in their expression levels (by stress).

The elevated expression of a group of genes important for lipid metabolism and detoxification were particularly notable.

Oestrogen Deactivation & Detoxification



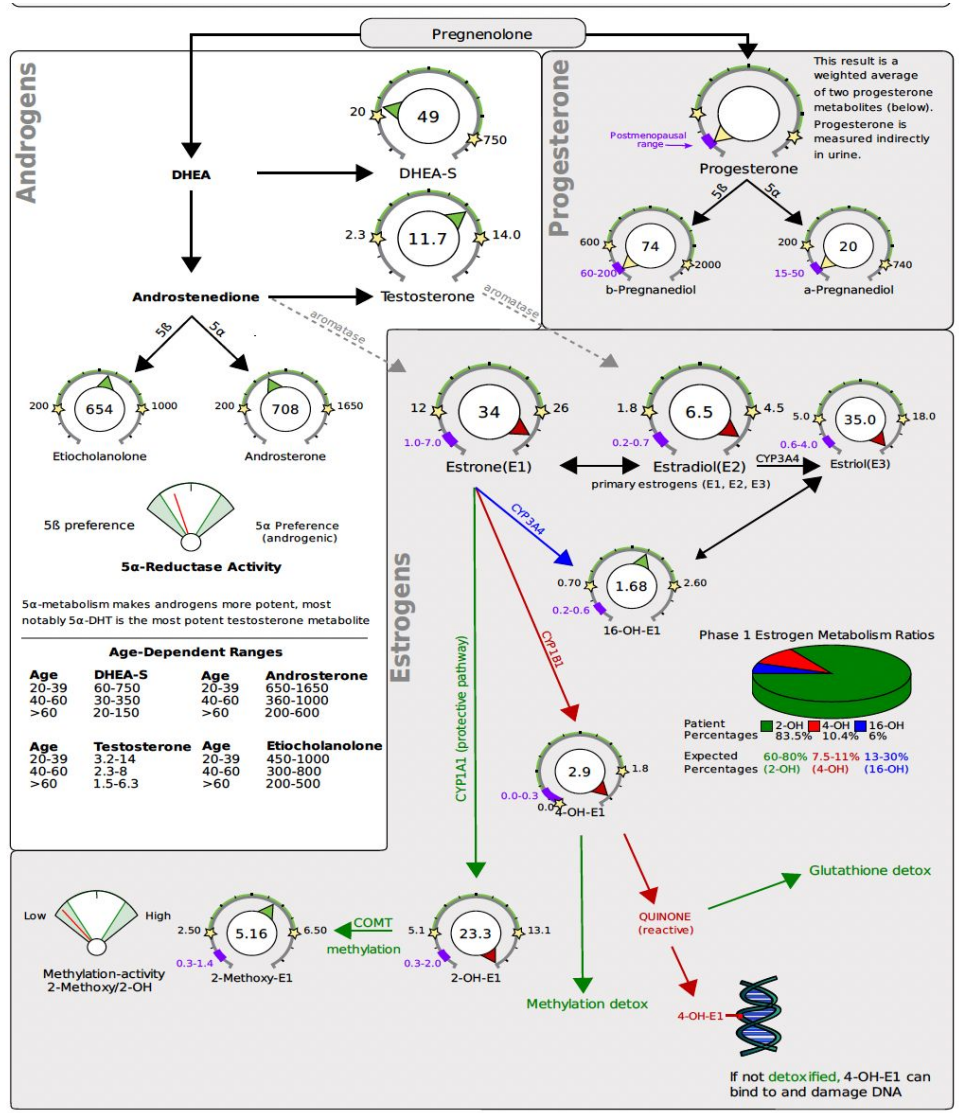
Phase 2 Conjugation

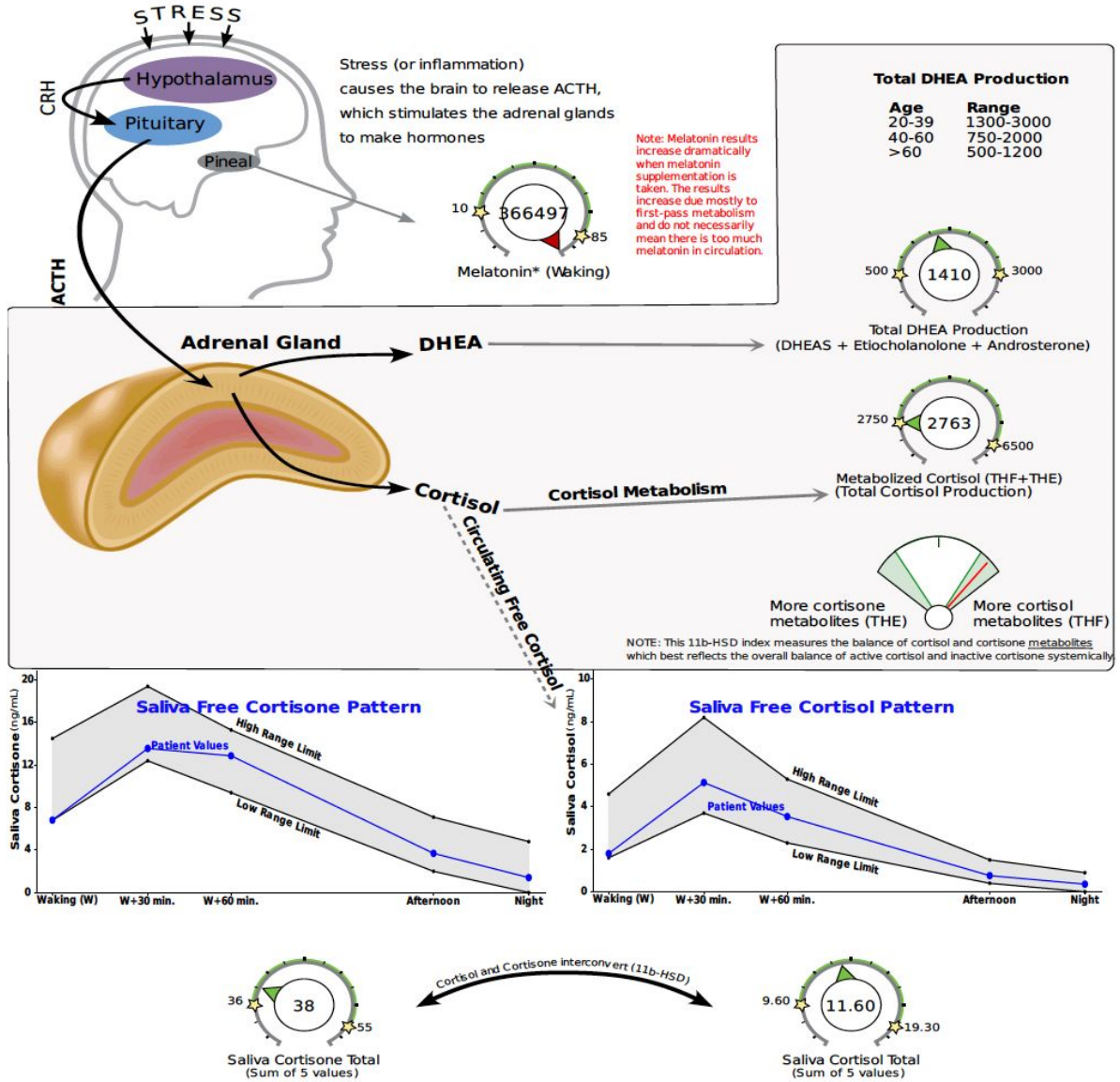
SULTs - Sulphonation/ Sulphation
UGTs - Glucuronidation
GSTs - Glutathione

Phase 3 AntiPorter

ABCB1 - MDRP1 (multi drug resistance protein)

https://www.researchgate.net/figure/Estrogen-metabolism-in-the-liver-and-in-the-ovarian-tumor-tissue-Oxidation-light-green_fig3_355138248


Pregnenolone
Androgens
DHEA
DHEA-S
20
49
750
Androstenedione
Testosterone
2.3
11.7
14.0
aromatase
5ß
5α
Etiocholanolone
200
654
1000
Androsterone
200
708
1650
5ß preference
5α Preference (androgenic)
5α-Reductase Activity
5α-metabolism makes androgens more potent, most notably 5α-DHT is the most potent testosterone metabolite
Age-Dependent Ranges
Age DHEA-S
20-39 60-750
40-60 30-350
>60 20-150
Age Androsterone
20-39 650-1650
40-60 360-1000
>60 200-600
Age Testosterone
20-39 3.2-14
40-60 2.3-8
>60 1.5-6.3
Age Etiocholanolone
20-39 450-1000
40-60 300-800
>60 200-500
Progesterone
This result is a weighted average of two progesterone metabolites (below). Progesterone is measured indirectly in urine.
Postmenopausal range
Progesterone
5ß
5α
600
74
2000
60-200
b-Pregnanediol
200
20
740
15-50
a-Pregnanediol
Estrogens
12
34
26
1.0-7.0
Estrone(E1)
1.8
6.5
4.5
0.2-0.7
Estradiol(E2)
CYP3A4
5.0
35.0
18.0
0.6-4.0
Estriol(E3)
primary estrogens (E1, E2, E3)
CYP3A4
CYP1B1
CYP1A1 (protective pathway)
0.70
1.68
2.60
0.2-0.6
16-OH-E1
Phase 1 Estrogen Metabolism Ratios
Patient Percentages 2-OH 83.5% 4-OH 10.4% 16-OH 6%
Expected Percentages 60-80% (2-OH) 7.5-11% (4-OH) 13-30% (16-OH)
2.9
1.8
0.0-0.3
4-OH-E1
Low
High
Methylation-activity
2-Methoxy/2-OH
2.50
5.16
6.50
0.3-1.4
2-Methoxy-E1
COMT
methylation
5.1
23.3
13.1
0.3-2.0
2-OH-E1
Methylation detox
QUINONE (reactive)
Glutathione detox
4-OH-E1
If not detoxified, 4-OH-E1 can bind to and damage DNA



The Cortisol Awakening Response (CAR) is the rise in salivary cortisol between the waking sample and the sample collected 30 (as well as 60) minutes later. This "awakening response" is essentially a "mini stress test" and is a useful measurement in addition to the overall up-and-down (diurnal) pattern of free cortisol throughout the day. **This patient shows a waking cortisol of 1.80 and an increase to 5.1 after 30.0 minutes. This is an increase of 3.34ng/mL or 186%.** Expected increases differ depending on the methods used. Preliminary research shows that 50-160% or 1.5-4.0ng/mL increases are common with samples collected 30 minutes after waking. These guidelines are considered research only.
This patient shows a salivary cortisol of 3.54 measured 60 minutes after waking. This is an increase of 1.74ng/mL or 96.7% compared to the waking sampe. To date, data suggests that expected results may be 0-70%, and this guideline is considered for research only.

CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION

Research Articles

Brassica Vegetable Consumption Shifts Estrogen Metabolism in Healthy Postmenopausal Women

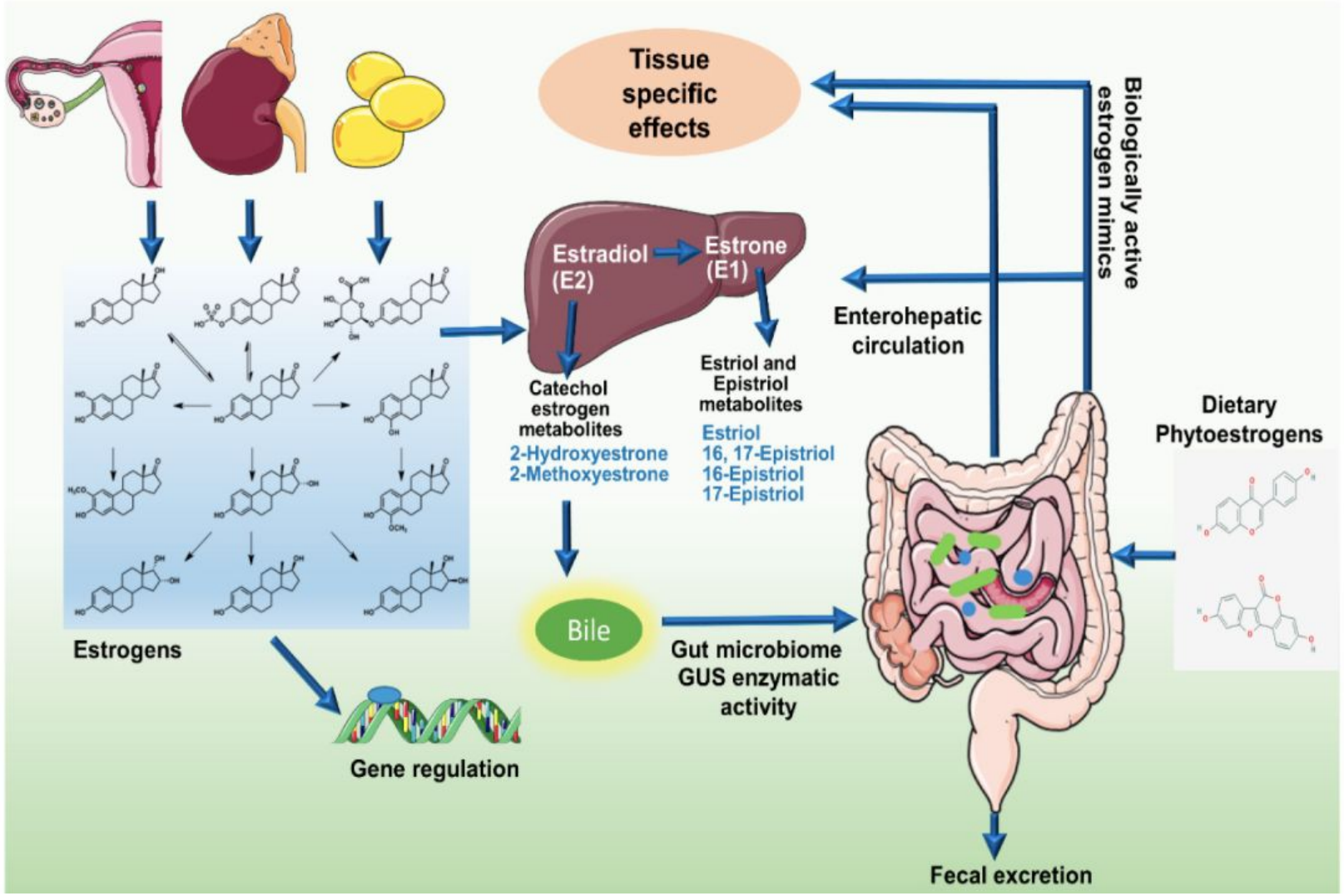
Jay H. Fowke, Christopher Longcope, and James R. Hebert

DOI: Published August 2000

August 2000
Volume 9, Issue 8

The results of this study indicate that the consumption of *Brassica* vegetables, as prepared and consumed by healthy postmenopausal women in the United States, was significantly

Fiber and the microbiome

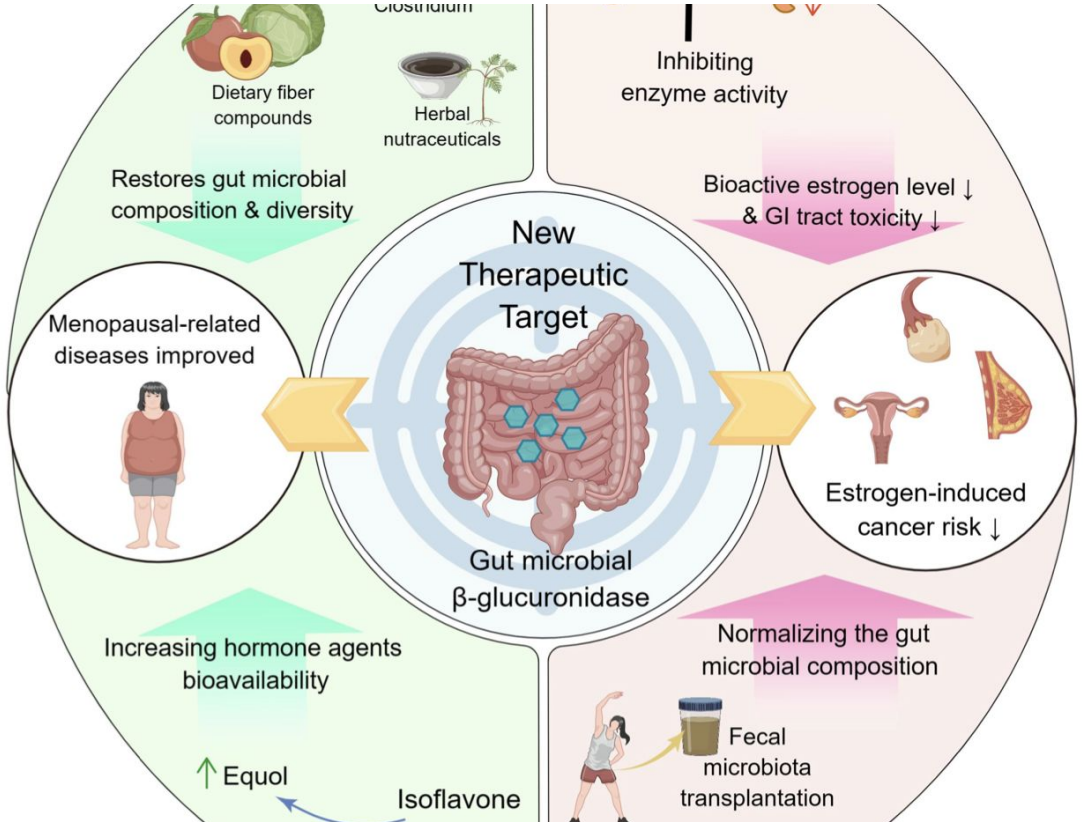


https://www.tandfonline.com/doi/abs/10.1080/01635581.2020.1784444?journalCode=hnuc20

Dietary Fiber

- Certain types of dietary fibers markedly enhance both phase
- I and II detoxification systems in the liver (rats)
- Higher fecal toxin excretion: via sequestering conjugated xenobiotic and endobiotics in the bile and this reduces level of bacterial deconjugating enzymes in stool.
- High fiber net effect: reduced enterohepatic circulation
- Microbiota – major detoxification facilitation
  - Fermentation of short chain fatty acids (butyrate, propionate, acetate)
  - provide colonocyte energy needs and genomic expression

Roland N J Nutr 1994 124:1581-7



by **Sheetal Parida** and **Dipali Sharma** *

Department of Oncology, Johns Hopkins University School of Medicine and the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD 21231, USA

* Author to whom correspondence should be addressed.

Cells **2019**, *8*(12), 1642; **https://doi.org/10.3390/cells8121642**

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Abstract

The microbiome is undoubtedly the second genome of the human body and has diverse roles in health and disease. However, translational progress is limited due to the vastness of the microbiome, which accounts for over 3.3 million genes, whose functions are still unclear. Numerous studies in the past decade have demonstrated how microbiome impacts various organ-specific cancers by altering the energy balance of the body, increasing adiposity, synthesizing genotoxins and small signaling molecules, and priming and regulating immune response and metabolism of indigestible dietary components, xenobiotics, and pharmaceuticals. In relation to breast cancer, one of the most prominent roles of the human microbiome is the regulation of steroid hormone metabolism since endogenous estrogens are the most important risk factor in breast cancer development especially in postmenopausal women. Intestinal microbes encode enzymes capable of deconjugating conjugated estrogen metabolites marked for

Foods and herbs that inhibit aromatase

- Dietary fiber
- Flax seeds
- Soy (isoflavones)
- Grape Seed extract (proanthocyanidins)
- White button mushroom
- Green tea
- Stinging nettle root
- Quercetin
- Vitamin C
- Chrysin
- Zinc

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3074486/

The physiological effect of a “cortisol steal”

- **Less progesterone** and initially an estrogen dominant state
- **More cortisol production and stimulation of aromatase, which leads to estrogen dominant conditions:**
  - Breast Cancer
  - Fibroids
  - Endometriosis
- **Long term decreased formation of androgens and estrogens**
- (inhibition of DHEA pathway to form androgens and estrogens)
  - Explains stress and hot flashes, stress and **decreased libido**

xenoestrogens

Medical Hypothesis: Xenoestrogens As Preventable Causes of Breast Cancer

Devra Lee Davis,[1] H. Leon Bradlow,[2] Mary Wolff,[3] Tracey Woodruff,[4] David G. Hoel,[5] and Hoda Anton-Culver[6]

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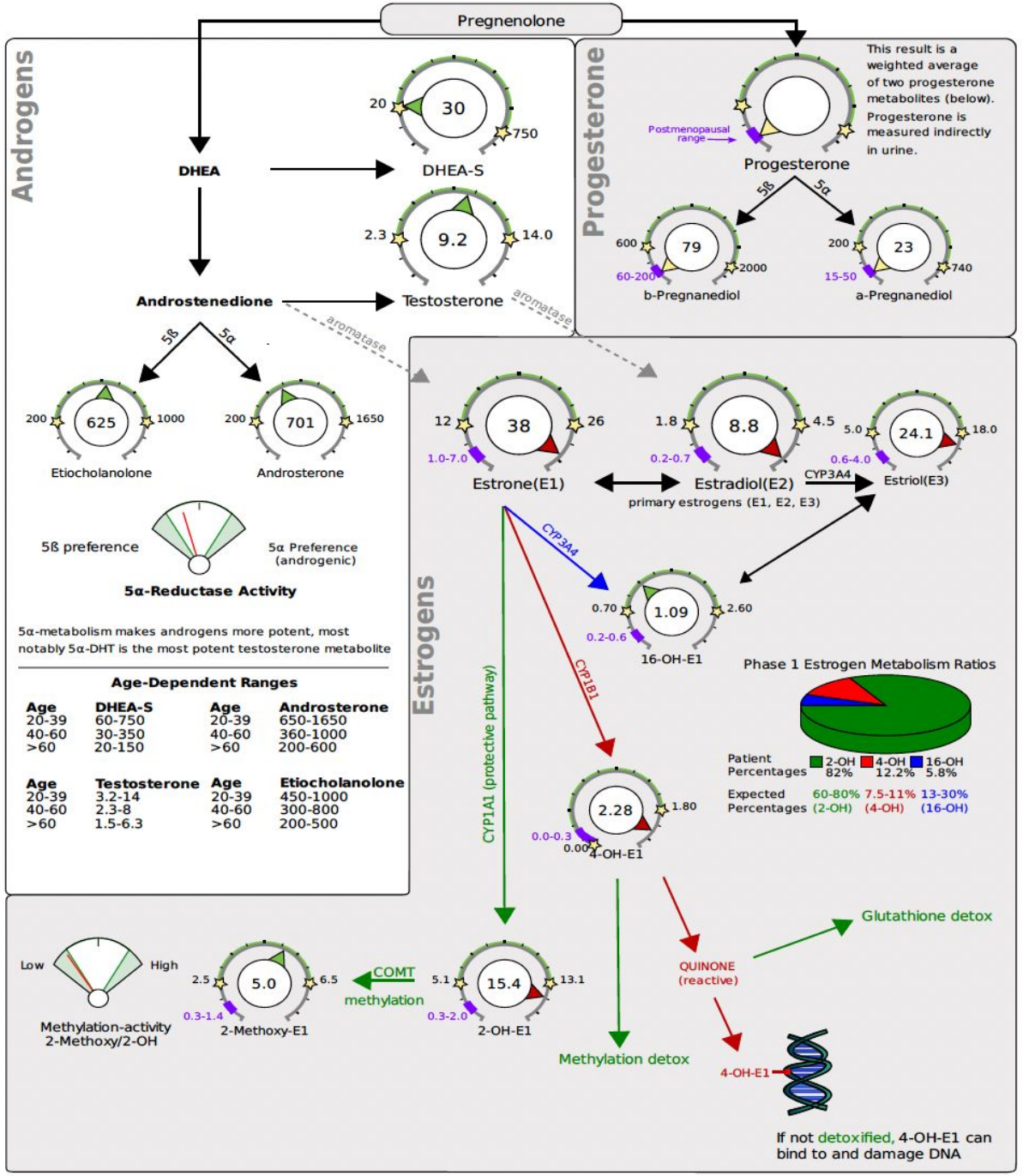
Changes in documented risk factors for breast cancer and rates of screening cannot completely explain recent increases in incidence or mortality. Established risk factors for breast cancer, including genetics, account for at best 30% of cases. Most of these risk factors can be linked to total lifetime exposure to bioavailable estrogens. Experimental evidence reveals that compounds such as some chlorinated organics, polycyclic aromatic hydrocarbons (PAHs), triazine herbicides, and pharmaceuticals affect estrogen production and

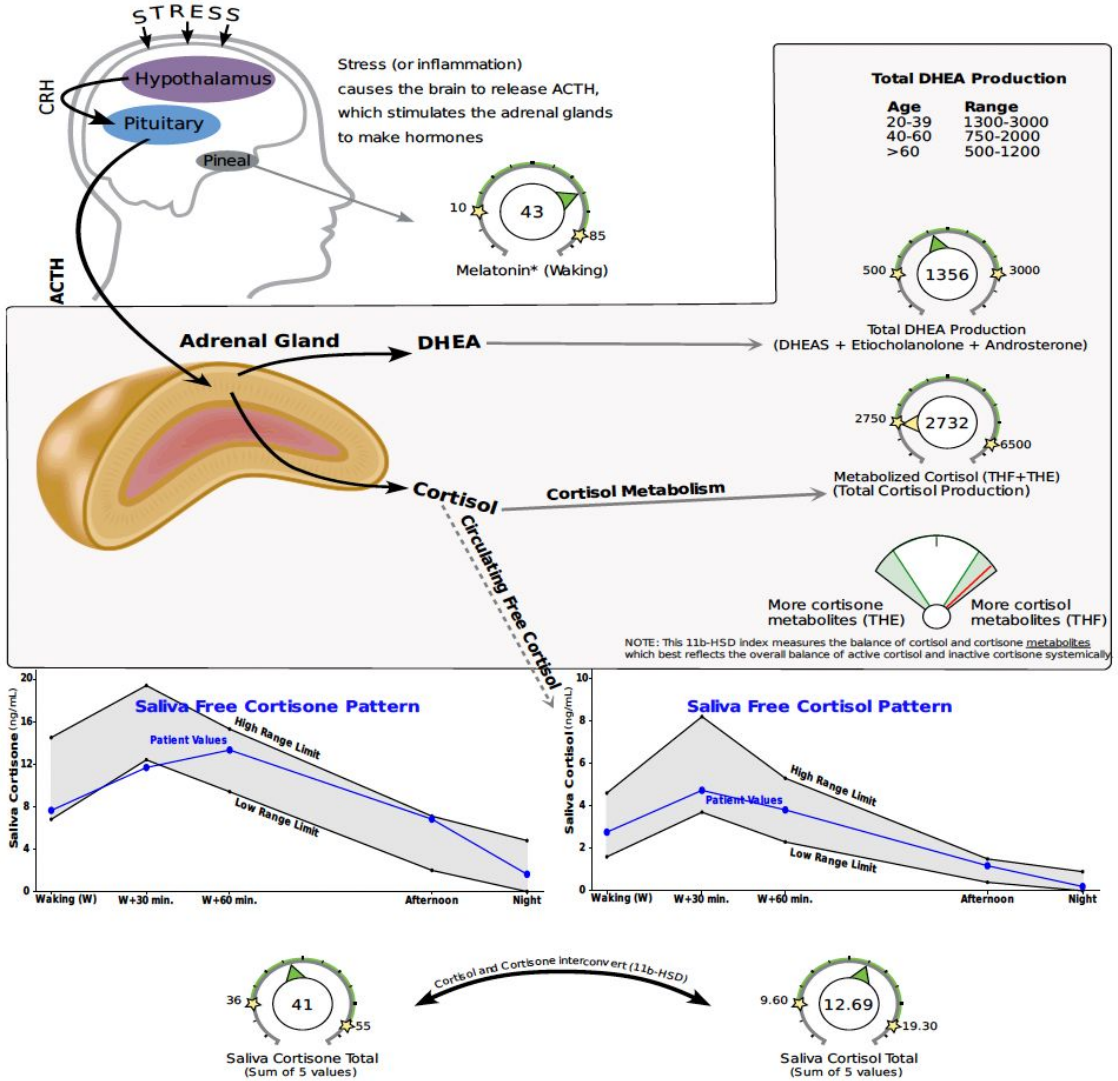
After years of puzzling, steady increases in breast cancer, public health researchers are rekindling interest in the role that exposure to xenobiotic agents, such as chlorinated organics and pharmaceutical agents, could play in the development of the disease. Do such substances increase the risk of this most common cancer in women by directly or indirectly altering estrogen production or metabolism? Do they activate or promote breast-cancer susceptibility

Experimental Evidence

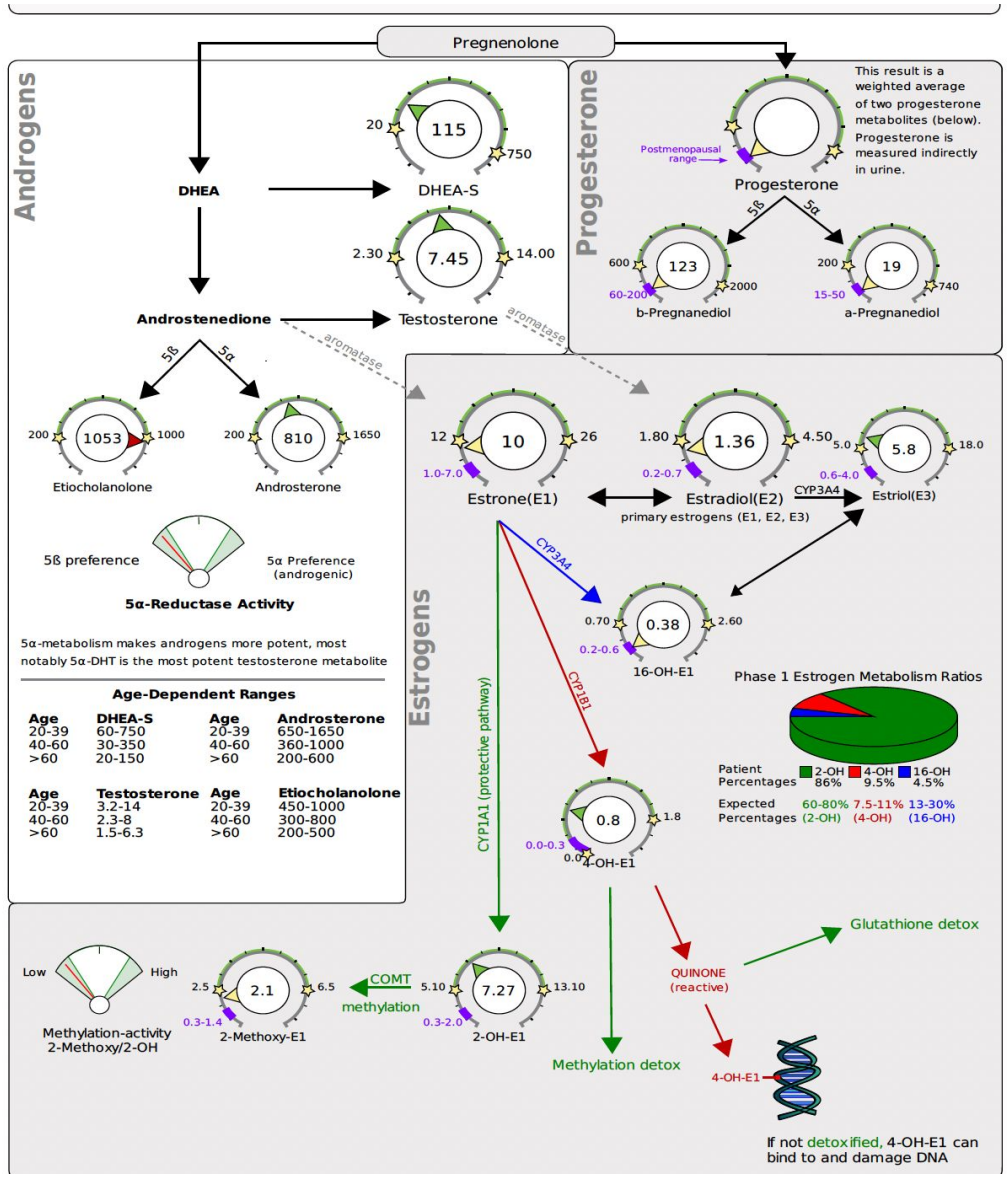
A number of lines of evidence attest to the ability of xenobiotic materials to affect estrogen production (*9*). Ovariectomy, which reduces endogenous hormones, inhibits the progression of chemically induced mammary tumors, whereas reintroduction of estrogen by implantation stimulates tumor development. Moreover, rat mammary cancers depend on both late and early exposure to estrogen and prolactin (*11*).

Experimental studies indicate that estradiol metabolism proceeds primarily via two mutually exclusive pathways, each of which is affected by xenobiotic exposures: pathway I to 2-hydroxyestrone (2-OHE1), which has minimal estrogenic activity and is nongenotoxic, or pathway II to 16α-OHE1, a fully potent estrogen which is also genotoxic (*12*). Breast cancer risk appears to be linked with these two pathways. Substances that elevate pathway II or inhibit pathway I increase risk, whereas those that inhibit pathway II or elevate


Pregnenolone
Androgens
DHEA
DHEA-S
20
30
750
2.3
9.2
14.0
Testosterone
Androstenedione
aromatase
aromatase
5ß
5α
200
625
1000
Etiocholanolone
200
701
1650
Androsterone
5ß preference
5α Preference (androgenic)
5α-Reductase Activity
5α-metabolism makes androgens more potent, most notably 5α-DHT is the most potent testosterone metabolite
Age-Dependent Ranges
Age DHEA-S
20-39 60-750
40-60 30-350
>60 20-150
Age Androsterone
20-39 650-1650
40-60 360-1000
>60 200-600
Age Testosterone
20-39 3.2-14
40-60 2.3-8
>60 1.5-6.3
Age Etiocholanolone
20-39 450-1000
40-60 300-800
>60 200-500
Progesterone
This result is a weighted average of two progesterone metabolites (below). Progesterone is measured indirectly in urine.
Postmenopausal range
Progesterone
5ß
5α
600
79
2000
60-200
b-Pregnanediol
200
23
740
15-50
a-Pregnanediol
Estrogens
12
38
26
1.0-7.0
Estrone(E1)
1.8
8.8
4.5
0.2-0.7
Estradiol(E2)
CYP3A4
5.0
24.1
18.0
0.6-4.0
Estriol(E3)
primary estrogens (E1, E2, E3)
CYP3A4
CYP1B1
CYP1A1 (protective pathway)
0.70
1.09
2.60
0.2-0.6
16-OH-E1
Phase 1 Estrogen Metabolism Ratios
Patient Percentages 2-OH 82% 4-OH 12.2% 16-OH 5.8%
Expected Percentages 60-80% (2-OH) 7.5-11% (4-OH) 13-30% (16-OH)
2.28
1.80
0.0-0.3
0.00
4-OH-E1
Low
High
Methylation-activity
2-Methoxy/2-OH
2.5
5.0
6.5
0.3-1.4
2-Methoxy-E1
COMT
methylation
5.1
15.4
13.1
0.3-2.0
2-OH-E1
Methylation detox
QUINONE (reactive)
Glutathione detox
4-OH-E1
If not detoxified, 4-OH-E1 can bind to and damage DNA



The Cortisol Awakening Response (CAR) is the rise in salivary cortisol between the waking sample and the sample collected 30 (as well as 60) minutes later. This "awakening response" is essentially a "mini stress test" and is a useful measurement in addition to the overall up-and-down (diurnal) pattern of free cortisol throughout the day. **This patient shows a waking cortisol of 2.76 and an increase to 4.73 after 30.0 minutes. This is an increase of 1.97ng/mL or 71.4%.** Expected increases differ depending on the methods used. Preliminary research shows that 50-160% or 1.5-4.0ng/mL increases are common with samples collected 30 minutes after waking. These guidelines are considered research only.
This patient shows a salivary cortisol of 3.81 measured 60 minutes after waking. This is an increase of 1.05ng/mL or 38.0% compared to the waking sampe. To date, data suggests that expected results may be 0-70%, and this guideline is considered for research only.


Pregnenolone
Androgens
DHEA
20
115
750
DHEA-S
2.30
7.45
14.00
Testosterone
Androstenedione
aromatase
aromatase
5ß
5α
200
1053
1000
Etiocholanolone
200
810
1650
Androsterone
5ß preference
5α Preference (androgenic)
5α-Reductase Activity
5α-metabolism makes androgens more potent, most notably 5α-DHT is the most potent testosterone metabolite
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Postmenopausal range
Progesterone
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5α
600
123
2000
60-200
b-Pregnanediol
200
19
740
15-50
a-Pregnanediol
Estrogens
12
10
26
1.0-7.0
Estrone(E1)
1.80
1.36
4.50
0.2-0.7
Estradiol(E2)
CYP3A4
5.0
5.8
18.0
0.6-4.0
Estriol(E3)
primary estrogens (E1, E2, E3)
CYP3A4
CYP1B1
CYP1A1 (protective pathway)
0.70
0.38
2.60
0.2-0.6
16-OH-E1
0.0-0.3
0.0
0.8
1.8
4-OH-E1
Phase 1 Estrogen Metabolism Ratios
Patient Percentages
2-OH 86%
4-OH 9.5%
16-OH 4.5%
Expected Percentages
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Low
High
Methylation-activity
2-Methoxy/2-OH
2.5
2.1
6.5
0.3-1.4
2-Methoxy-E1
COMT
methylation
5.10
7.27
13.10
0.3-2.0
2-OH-E1
Methylation detox
QUINONE (reactive)
Glutathione detox
4-OH-E1
If not detoxified, 4-OH-E1 can bind to and damage DNA

Managing stress positively

- Relaxation techniques
- Lifestyle strategies
- Exercise
- Sleep
- Targeted nutrients
- Diaphragmatic breathing
- Meditation
- Yoga

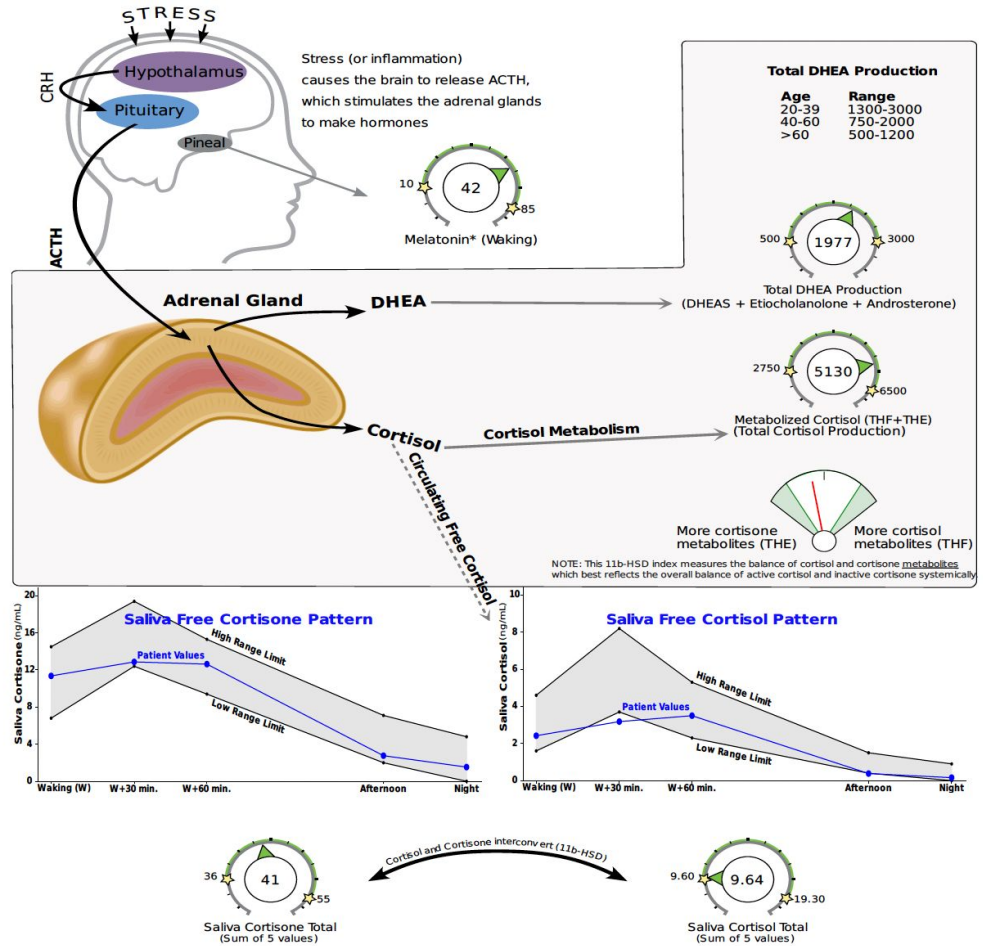
Magnesium and Sleep

Magnesium improves duration and quality of sleep

- Double-blind randomized clinical trial; 46 elderly subjects
  - 500 mg of magnesium oxide (225mg elemental Mg) or placebo daily for 8 weeks.
- **<u>Significant improvements in:</u>**
  - Sleep duration
  - Sleep efficiency
  - ↓ sleep latency
  - ↓ serum cortisol

Parameter	% Change over baseline*	
	Supplement	Placebo
Insomnia severity index	−14.4 (−31.6, 2.8)[a,b]	−2.7 (−7.2, 1.6)
Total sleep time (h)	3 (−1.8, 7.6)	−0.19 (−2.3, 1.9)
Sleep time (h)	12 (5.2, 18.9)[a,b]	−0.27 (−2.7, 2.2)
Sleep onset latency (h)	−14 (−30.8, 2.7)[a,b]	3.7 (−1.0, 8.4)
Early morning awakening (h)	−3 (−5.1, −0.8)[a]	−1.0 (−1.7, −0.3)
Sleep efficiency (h)	9.6 (2.5, 16.7)[a,b]	0.1 (−2.9, 3.1)
Serum magnesium (mmol/l)	4.2 (−0.2, 8.5)	−1.3 (−5.5, 2.9)
Serum renin (mIU/ml)	36.7 (18.2, 55.2)[a,b]	−5.9 (−13.8, 1.9)
Serum melatonin (pg/ml)	35 (10.5, 59.5)[a,b]	−1.1 (−23.6, 21.3)
Serum cortisol (μg/dl)	−8.2 (−19.6, 3.1)[a,b]	3.5 (−0.48, 7.6)

[a]% change over baseline significant ($P<0.05$); [b]% change over baseline significantly higher than control ($P<0.05$); *Figures in parentheses show 95% confidence interval for mean



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ANY
QUESTIONS?

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