The Estrogen Gene Test

Scientific Rationale and Clinical Guidelines

ABSTRACT

It is now well-documented that a woman's cumulative exposure to estrogen throughout her life is associated with her risk of breast cancer.[1] Developed countries have and will continue to use exogenous estrogen medications such as oral contraception[2], hormone replacement therapy (HRT)[3,4], bio-identical supplementation and fertility medications.[5] Indeed, HRT is still prescribed despite large studies from the Women's Health Initiative[3] and the European Prospective Investigation into Cancer[4] demonstrating increased breast cancer risk. Especially concerning is the current trend of an increasing incidence of estrogen receptor-positive breast cancers, with epidemiologists from the National Cancer Institute projecting a rise from 158 to 166 cases per 100,000 women in the U.S. by the year 2016.[6]

Many prominent scientists including James Yager and Nancy Davidson have drawn attention to what is known as the dual carcinogenetic mechanism of estrogen. In addition to fueling estrogen receptor-positive breast cancers, estrogens enhance cell proliferation and act as genotoxic precursors.[1,7] Over the last several years, the enzymatic pathways responsible for metabolism and detoxification have been characterized. Concurrent efforts have mapped single nucleotide polymorphisms (SNPs) in several estrogen metabolism genes that confer an increased risk of breast cancer. Breakthrough studies from Vanderbilt University[8], the University of Alberta[9], Harvard[10], and others[11,12], have found significant, synergistic interactions between specific groups of estrogen metabolism SNPs in association with breast cancer. These groups of SNPs simulate well-defined carcinogenetic mechanisms within the estrogen metabolism pathway.

Importantly, these SNPs are not included in the traditional handful of familial breast cancer susceptibility genes such as BRCA1 and BRCA2. Familial genes account for less than 20% of breast cancers.[13] The SNPs of interest occur in six estrogen metabolism genes. Interestingly, one SNP is not sufficient to increase the risk of breast cancer, but the interaction of two or more SNPs can increase breast cancer risk from 2.5 to as much as 13 fold.[11]

The **Estrogen Gene Test** is a simple saliva test that can be used to identify polymorphisms in all of the key estrogen metabolism genes: Cytochrome P450 enzymes (CYP1A1, CYP1B1, and CYP3A4), catechol-O-methyltransferase (COMT), glutathione-S-transferase (GST), and manganese superoxide dismutase (MnSOD). The Estrogen Gene Test is a unique tool that can identify patients who inappropriately metabolize estrogen and related compounds. While every woman should have an Estrogen Gene Test performed at some point, the test is particularly important in women who are considering oral contraceptives, hormone replacement therapy, bio-identical supplementation, in vitro fertilization, or who have been diagnosed with estrogen receptor-positive breast cancer. With this knowledge in hand, clinicians can mitigate breast cancer risk through targeted nutritional and lifestyle interventions.

Author Summary

Estrogen is a critical hormone for the growth, development, sexual maturity, and reproductive ability of women

Estrogen is also toxic to women in high amounts

Roughly 65% of breast cancers are estrogen receptor positive and are fueled by estrogen

Estrogen and its metabolites can lead to carcinogenesis by inducing cell proliferation and by direct genotoxicity

Known familial breast cancer genes such as BRAC 1/2 and familial susceptibility genes are responsible for at most 20% of breast cancers

Estrogen metabolism genes may provide more clarity into the mechanism of as much as 65% of breast cancer which is estrogen receptor positive

While mutations on single estrogen metabolism genes do not seem to raise the risk of breast cancer; women who possess two or more of particular SNPs in this metabolic pathway have from a 2.7 to 12 fold increased risk of breast cancer

Importantly, the gene expression of estrogen metabolism genes may be upregulated or downregulated through individualized nutritional and behavioral interventions

The Estrogen Gene Test is a simple saliva test that determines which SNPs may be present and recommends protocols to upregulate or downregulate gene expression

The Estrogen Gene Test provides clinicians with an indispensible tool in improving the safety of prescribing estrogen based medications for their patients

The Estrogen Gene Test allows clinicians to target exactly the right patients with increased breast cancer monitoring and with the tools to prevent more breast cancer in their patients

Clinicians should consider the Estrogen Gene Test for future, current and past users of HRT, Bio-Identicals, IVF medications, OCP's, ER+ breast cancer survivors and women with a family history of ER+ breast cancer

By recommending protocols to improve estrogen metabolism and monitoring those efforts through urinary estrogen metabolites, clinicians have, for the first time, a chance to prevent breast cancer on an individual basis

Early research into breast cancer genetics consisted of linkage studies within families with a history of breast malignancies. This extensive work revealed 8 familial breast cancer susceptibility gene mutations, including the highly-penetrant BRCA1 and BRCA2 gene mutations.[13] However, these gene mutations explained roughly 20% of breast cancers of the population as a whole.[13] Subsequent linkage analyses proved to be tenuous and inconsistent for a number of reasons; most importantly, the majority of both familial and sporadic breast cancers are caused by mutations in multiple, low-penetrance genes. In fact, recent statistics from the American Association for Cancer Research show that only 10% of all breast cancers are due to polygenic susceptibility and unknown gene mutations and the majority of sporadic cancers are likely caused by multiple, low-penetrance gene mutations.[14] Thus, the vast majority of breast cancers are not currently predictable by standard genetic testing. Long before the BRAC gene work, scientists had been exploring the relationship between estrogen metabolism genes and breast cancer. Ritchie and colleagues from Vanderbilt University published a breakthrough analysis of high-order SNP interactions and breast cancer.[15] They studied 200 women with sporadic breast cancer using a gene interaction model of various estrogen metabolism genes including COMT, CYP1A1, CYP1B1, GSTM1, and GSTT1. The group identified specific combinations of SNPs (using a process called multifactor-dimensionality reduction) that were prevalent among women with breast cancer.[15] Researchers from the University of Ljubljana in Slovenia, extended this work to include other estrogen metabolism genes, CYP1B1, COMT, GSTP1, and MnSOD.[11] Importantly, none of the four genetic variants significantly contributed to breast cancer risk on their own, but when present in certain combinations (even as few as two of the right kind) could increase the risk of breast cancer from 2.7- to 13-fold—a remarkably strong indicator of risk.[11] These results have been confirmed in many another studies examining outcomes in thousands of women.[8,9,12,16]

Single gene SNPs have no appreciable effect on breast cancer risk, but women who possess a certain combination of SNPs have from 2.5 to 13-fold increased risk of breast cancer

Subsequent and parallel studies shed light on the functional consequences of these SNP combinations. Particular SNP combinations increased the risk of breast cancer, to be sure, but they also change the kinetics of the corresponding enzyme variants. In other words, if a woman possesses a particular set of SNPs in her estrogen metabolism genes she has predictable changes in her estrogen metabolism. Women who possessed the SNPs associated with increased risk of breast cancer also had elevated rates of carcinogenic estrogen metabolite formation.[8,17] **Therefore, the presence of certain SNPs in a woman's estrogen metabolizing genes predicts the way that she metabolizes estrogens and her breast cancer risk**.

ESTROGEN: THE GOOD AND THE BAD

Estrogen serves a number of critical roles in the human body, from sexual differentiation and development to the regulation and coordination of reproductive function. It is one of the most potent bioactive molecules known to man. Estrogen and its related steroid molecules (e.g. progesterone) have been used reliably as birth control for decades. Unfortunately, this potency and power comes with a price for women. We know that estrogen exposure can be a risk factor for cancer. For example, women who are exposed to higher levels of endogenous estrogen, such as those who have earlier menarche, are older at first pregnancy or at menopause have a higher risk of developed breast cancer.[1] Likewise, women who take exogenous estrogen in the form of hormonal contraceptives, hormone replacement therapy (HRT), bio-identical supplementation or fertility regimens also have higher rates of breast cancer.[18,19]

ENDOGENOUS ESTROGEN EXPOSURE

Cumulative exposure to endogenous estrogen throughout a woman's life correlates with the risk of breast cancer and is a major risk determinant.[1,20] Prominent epidemiologists, such as Key and colleagues, have shown that women with higher serum levels of endogenous estrogen have a 2- to 2.58-fold increased risk of breast cancer.[21] This cumulative exposure, linked to a woman's reproductive lifespan, is an index of estrogen exposure and an important risk modifier. For every 1-year delay in the onset of menarche, there is a 5% lifelong risk reduction in breast cancer[22], and every 1-year delay in menopause onset is associated with a subsequent 3% increased risk of breast cancer.[23] Additionally, women who have had at least one full-term pregnancy have a 25% lower risk of breast cancer women than who have never given birth.[24,25]

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EXOGENOUS ESTROGENS: ORAL CONTRACEPTIVES & HORMONE REPLACEMENT THERAPY

The Collaborative Group on Hormonal Factors in Breast Cancer conducted a large meta-analysis of 53,297 women with breast cancer (100,239 controls) and found that women taking combined oral contraceptives had a greater risk of breast cancer—an effect that extended 10 years after cessation of use.[2] This same group then reanalyzed results from 52,705 postmenopausal women with breast cancer and found a significantly increased, cumulative risk of breast cancer among HRT recipients for up to 5 years of treatment.[23] The acclaimed Women's Health Initiative (WHI) was subsequently launched in 1993 to examine the effects of 2 main types of HRT (combined estrogen-progestin versus estrogen-only) on health outcomes in 27,347 postmenopausal women. The combined HRT versus placebo arm of the study was stopped early due to a significant increased incidence of breast cancer among combined HRT recipients.[3] The WHI outcomes are in agreement with a cross-sectional study of 54,548 French postmenopausal women from the European Prospective Investigation into Cancer (EPIC), wherein combined HRT was significantly associated with breast cancer.[4] According to Anderson and colleagues from the National Cancer Institute, a sharp

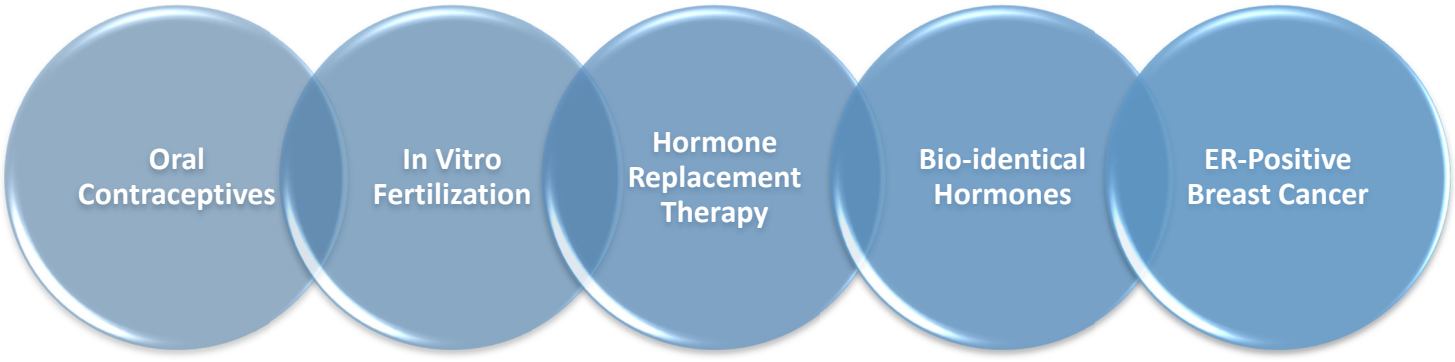
drop in the incidence of breast cancers between the years 2000 and 2003 was due to awareness of the association of hormone replacement therapy (HRT) with breast cancer following these important studies.[6] However, this decrease has since plateaued, perhaps due in part to the emergence of bioidentical hormone use to replace traditional HRT. Importantly, there is no evidence to suggest that these compounded hormones are safer than traditional HRT either in cardiovascular or breast cancer risk.[26]

FERTILITY TREATMENTS

Diethylstilbestrol, a currently banned fertility drug, was associated with a 30% increased incidence of breast cancer among women who were treated between the 1940's and the 1960's.[27] Studies examining the effects of subsequently used fertility regimens have been hampered by small sample sizes, suboptimal (mostly retrospective/observational) designs, lack of adjustment for confounding variables (e.g. other breast cancer risk factors), lack of stratification by type of fertility drug, dose increments, and short follow-up duration.[28,29,30,31] Nevertheless, women who undergo hormonal treatments associated with IVF are exposed to concentrations of estrogens as high as 20 times endogenous circulating levels. In a prospective, cross-sectional study by Venn and colleagues from the Centre for the Study of Mothers' and Children's Health in Australia, 20,656 women treated with superovulation drugs for in-vitro-fertilization (IVF) were compared to 9,044 unexposed women. A significant 1.96-fold increased risk of breast cancer was found in treated women within 12 months of exposure to superovulation drugs.[19] Data from the prospective cross-sectional EPIC study showed a significant increased risk of breast cancer among recipients of fertility drugs who had a first-degree relative with a history of breast cancer, or who had a personal history of benign breast disease. Gauthier and others reporting for the E3N group found an overall increased risk of breast cancer in women with a family history of breast cancer who had fertility treatments;[5] suggesting that families with clusters of breast cancer are "more sensitive to hormonal factors."[5,32]

ESTROGEN RECEPTOR-POSITIVE BREAST CANCER

Perhaps the most well-known effect of estrogens and breast cancer is in patients with estrogen receptor-positive breast cancer. These tumors express functional hormone receptors that, when stimulated by circulating estrogens, promote cell proliferation. Therapy is aimed at lowering circulating hormone levels and blocking the effects of estrogen on tumor cells.



The favorable elimination of estradiol metabolites requires that they be converted to water-soluble molecules by COMT and GST; COMT conjugates them with methyl groups, whereas GST conjugates them with glutathione groups. The pathway that predominates under normal circumstances is the conversion of estradiol into 2-OHE_1 by CYP1A1. 2-OHE_1 is readily metabolized into 2-MethoxyE_2 for elimination. The carcinogenic pathways involve conversion of estrone into 16α-OHE_1 by CYP3A4, and into 4-OHE_1 by CYP1B1. 16α-OHE_1 is highly available to target cells and stimulates cell proliferation, thus favoring carcinogenesis. In addition, 4-OHE_1 is more readily oxidized into semiquinones and quinones; which produces carcinogenic free radicals. Quinone molecules are known to form mutagenic adducts with DNA. MnSOD is an enzyme that detoxifies free radicals into H_2O_2 and O_2.

Figure 2 - Oxidative Metabolism of Estrogens

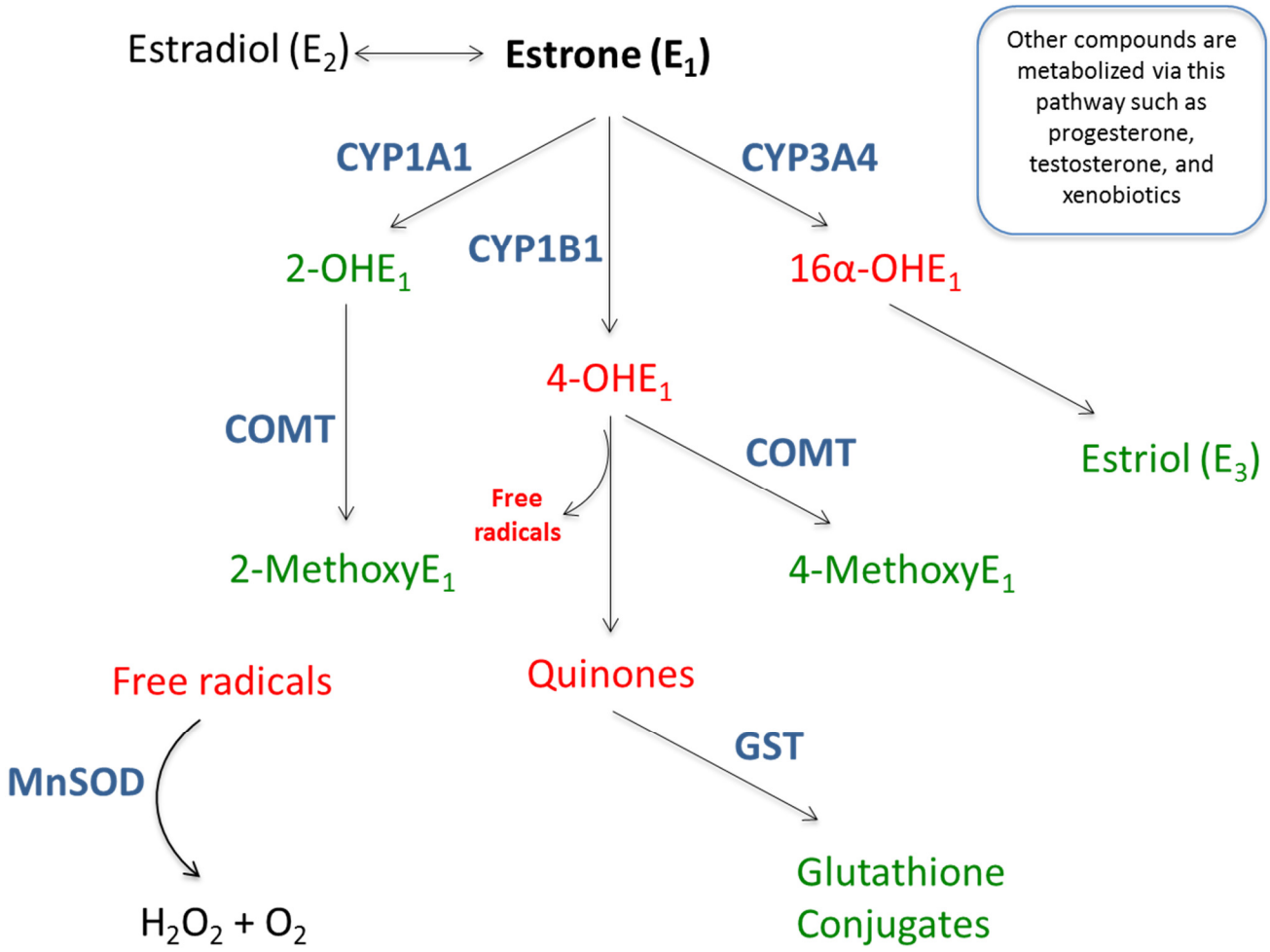
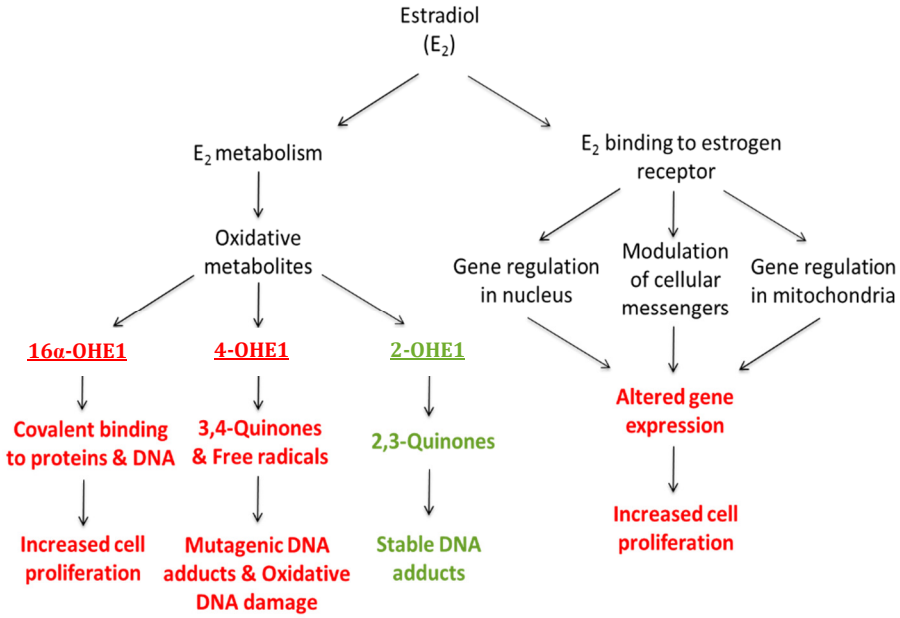


Figure 2. The six estrogen metabolism genes or their encoded enzymes are shown in blue. Carcinogenic metabolites and their products are shown in red and anticarcinogenic or neutral metabolites and their products are shown in green. CYP1A1, CYP1B1, and CYP3A4 are enzymes of the cytochrome P450 family; COMT, catechol-O-methyltransferase; GST, glutathione-S-transferase; MnSOD, manganese superoxide dismutase; E_2, estradiol; H_2O_2, hydrogen peroxide; O_2, oxygen.

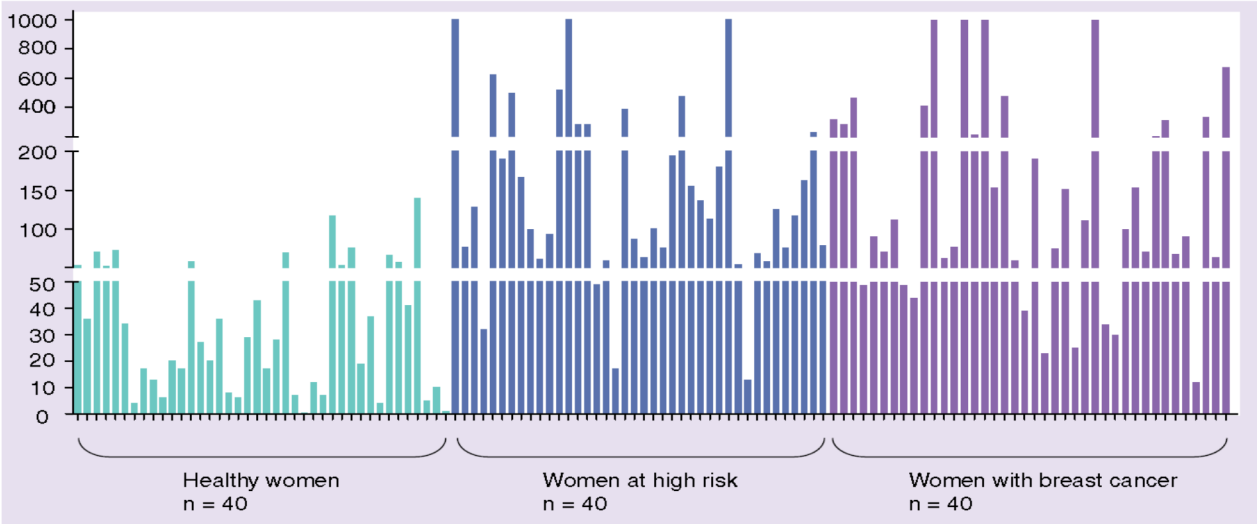
Estrogens can promote carcinogenesis in at least two ways. The steroid hormones are proliferative, so they can increase target cell proliferation. While this might be useful in normal endometrial tissue, it can be damaging in the case of estrogen receptor positive breast cancer.

Figure 3 – The Dual Carcinogenic Mechanism of Estrogens



The other way that estrogens are carcinogenic is that they exert direct genotoxic effects. Certain estrogen metabolites form free radicals and mutagenic adducts with DNA (Figure 4).[1]

Figure 4 – Estrogen-DNA Adducts and Breast Cancer



Ratio of depurinating estrogen-DNA adducts to estrogen metabolites/conjugates. 4-OHE1-DNA adducts are responsible for >98% of the ratio. Ratios are much higher in women with breast cancer or who are at high risk for developing breast cancer. Adapted from Cavalieri and Rogan, 2010.[33]

The Estrogen Gene Test, performed on a sample of saliva, identifies single nucleotide polymorphisms, or SNPs, in 6 genes involved in estrogen metabolism (Figure 5). These SNPs and their encoded enzyme variants determine circulating levels of estrogen and estrogen metabolites.[7] A woman's particular profile of SNPs predicts a modifiable component of her overall risk of developing breast cancer.

Figure 5 – SNPs of the Estrogen Gene Test

CYP1A1 — **Cytochrome P450 1A1**

- Fast metabolizers efficiently convert a potentially carcinogenic estrogen, **Estrone**, to a more desirable estrogen metabolite, **2-OHE$_1$**

CYP1B1 — **Cytochrome P450 1B1**

- Fast metabolizers favor the conversion from estrone to a potentially carcinogenic estrogen, **4-OHE$_1$**

CYP3A4 — **Cytochrome P450 3A4**

- Fast metabolizers quickly convert estrones to potentially carcinogenic estrogens, **4-OHE$_1$** and **16-OHE$_1$**

COMT — **Catechol-O-methyltransferases**

- Slow metabolizers do not convert the potentially carcinogenic estrogen **4-OHE$_1$** to the more favorable **4-MeOE$_1$**

GSTP1, GSTM1, GSTT1 — **Glutathione-S-transferases**

- Slow metabolizers or gene deficient individuals do not convert the potentially carcinogenic estrogen **4-OHE$_1$** to the more favorable **Glutathione Conjugates**

MnSOD — **Manganese superoxide dismutase**

- Reduced MnSOD enzyme activity is associated with potentially genotoxic **Free Radical** formation

An important attribute of the EGT panel enzymes is their ability to detoxify intracellular products of oxidative reactions. These enzymes must metabolize a myriad of xenobiotics (harmful exogenous compounds found in some foods and most environmental pollutants) while also metabolizing estrogen. The cytochrome P450 enzymes, CYP1A1, CYP1B1, and CYP3A4, are able to activate xenobiotics, including polycyclic aromatic hydrocarbons (PAHs), heterocyclic amines (HAs), 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), aflatoxin B1, and nitrosamines, into carcinogenic compounds.[33,34,35] Catechol-O-methyltransferase (COMT) and glutathione-S-transferase (GST) can detoxify a variety of xenobiotics and ROS[36,37], while manganese superoxide dismutase (MnSOD) converts superoxide free radicals to hydrogen peroxide.[38] Thus, not only does the woman with certain SNPs face the burden of toxic estrogen metabolites, part of the overall increased breast cancer risk in these women may be due to the reduced ability to detoxify xenobiotics.

A woman's particular profile of estrogen metabolism SNPs, provides a powerful tool for intervention to decrease her risk of developing breast cancer

The genes tested in the Estrogen Gene Test may be regulated through nutritional and lifestyle interventions. By altering the estrogen metabolism and lowering the circulating levels of estrogens, it is possible to mitigate the risk of breast cancer development or breast cancer recurrence. Overall, a large body of evidence supports the chemopreventive potential of specific nutritional and behavioral interventions, through gene regulation and metabolic pathway modulation.

Table 1 – The Estrogen Gene Test: SNPs and Treatment

Gene	Result of SNP	What Does the Gene do?	Frequency in the population	Nutritional Intervention	Lifestyle Intervention
CYP1A1	Rapid metabolizer	Converts estrone, a potentially carcinogenic estrogen, to a more desirable estrogen metabolite (2-0HEl). Slow metabolizers can potentially have higher levels of estrone and lower levels of 2-0HEl due to slower conversion.	9% Caucasians 22-25% African Amer. 42% East Asians	DIM-Pro for Wild Type/Normal	Avoid cigarette smoke, charbroiled meats, PAHs
CYP1B1	Rapid metabolizer	Converts estrone, a potentially carcinogenic estrogen, to a potentially carcinogenic intermediate (4-0HEl). Fast metabolizers can potentially have higher levels of 4-0HEl.	46% Caucasians 68% African Amer. 17% East Asians	DIM-Pro, DHEA, Fish oil, Flaxseed	None
CYP3A4	Rapid metabolizer	Converts estrone, a potentially carcinogenic estrogen, to a potentially carcinogenic intermediate (16aOHE1). Fast metabolizers can potentially have higher levels of 16a-0HE1.	4-10% Caucasians 48-80% African Amer. 0% East Asians	DIM-Pro	None
COMT	Slow metabolizer	Converts intermediate estrogen metabolites to excretable forms (2-0HE1 to 2-MeEl and 4-0HEl to 4-MeEl). Slow metabolizers may clear estrogen metabolites less efficiently.	39-63% Caucasians 35% African Amer. 21-34% East Asians	SAM-E	Stress reduction. Avoid excess alcohol intake
GSTP1	Slow metabolizer	Converts toxic intermediate metabolites (quinones) to more desirable by-products (glutathione conjugates). Those with reduced or no activity can potentially have higher levels of toxic estrogens.	23-35% Caucasians 42-45% African Amer. 14-26% East Asians	Antioxidants: L-Glutathione, NAC, Vit A, Vit C, Vit E, Selenium, Milk thistle, Colorful fruits, Cruciferous vegetables	Avoid herbicides, fungicides, insect spray, industrial solvents, smoke, mercury, cadmium, lead
GSTM1	Absent enzyme		38-54% Caucasians 22-35% Africans 35-62% East Asians		
GSTT1	Absent enzyme		11-18% Caucasians 24% African Amer. 38-58% East Asians		
MnSOD	Less available in mitochondria	Scavenges oxygen free radicals that can damage DNA. Reduced activity increases risk for cancer, especially if antioxidants are low	50% Caucasians 45% African Amer. 14% East Asians		None

PAH, polycyclic aromatic hydrocarbons; SAM-E, S-adenosyl methionine; NAC, N-acetylcysteine; DIM, diindolylmethane complex; DHEA, dehydroepiandrosterone

The Estrogen Gene Test gives clinicians a way to assess and intervene in breast cancer on a personalized level in a way that has never before been possible

DIM-PRO

Indole-3-carbinol (I3C) and the product of its dimerization in gastric fluid, diindolylmethane (DIM), are compounds with various anticarcinogenic modulatory effects. A study by Michnovicz and colleagues demonstrated the induction of CYP1A1 by I3C in human subjects, resulting in an increased production of the anti-carcinogenic estrogen metabolite 2-OHE_1.[39] Upon treatment of human breast cells with I3C, Telang and others reported a decrease in 2-OHE_1/16α-OHE_1 ratios, an increase in cell cycle arrest and apoptosis, and the inhibition of cell proliferation.[40] Chen and colleagues also demonstrated the ability of DIM to antagonize the aryl hydrocarbon receptor (a xenobiotic receptor that induces CYP1A1 to activate xenobiotics into carcinogens), and to inhibit estrogen receptor (ER)-mediated cell proliferation in human breast cancer cells.[41] Furthermore, Gross-Steinmeyer and colleagues from the University of Washington in Seattle reported a downregulation in CYP3A4 expression leading to the inhibition of aflatoxin B1 activation into carcinogens in human liver cells treated with DIM.[42] According to a review paper by Bradlow, DIM should be the chemoprotective supplement of choice, as it has a safer and more predictable action profile than its precursor, I3C.[43]

CRUCIFEROUS VEGETABLES

Cruciferous vegetables are any of the mustard family of beaked cylindrical pods, including cabbage, broccoli, turnips, and mustard and are key sources of I3C (and DIM, after digestion). Cruciferous vegetables also provide isothiocyanates that act as co-substrates for and inducers of GST glutathione conjugation reactions. This enhances metabolism of toxic estrogen metabolites. In a study from the Fred Hutchinson Cancer Research Center in Seattle, WA, humans who consumed cruciferous vegetables had increased serum concentrations of GST enzymes, an effect that was particularly marked in people with GSTM1 and GSTT1 deletion SNPs.[44]

OMEGA-3 POLYUNSATURATED FATTY ACIDS (Ω-3-PUFAS)

Omega-3 polyunsaturated fatty acids (Ω-3-PUFAs), found in fish oils, have been shown to counter the carcinogenic effects of Ω-6-PUFAs and other inflammatory mediators implicated in breast carcinogenesis. In a study from the University of Texas M. D. Anderson Cancer Center, mutagenic etheno-DNA adducts, derived from Ω-6-PUFA peroxidation by 4-OHE_2-generated free radicals, were detected at 3-fold higher levels in breast tissue from breast cancer patients compared to cancer-free controls.[45] Medeiros and colleagues from the Kansas State University were able to demonstrate selective cell membrane incorporation of Ω-3-PUFAs over their Ω-6 counterparts in various tissues in rats fed with Ω-3-PUFA-enriched beef.[46] Ω-3-PUFAs were also found to suppress the activity of cyclooxygenase-2 (a key enzyme that catalyzes the metabolism of Ω-6-PUFAs into inflammatory prostanoids)[47] and to inhibit the production of nitric oxide (a mediator of cell injury during inflammation).[48] Supplementation with fish oil can therefore boost the Ω-3-: Ω-6-PUFA ratio and may counter the carcinogenic effects of oxidative inflammation in states of 4-OHE_1 overproduction, as in carriers of CYP1B1 rapid-metabolizer SNPs.

DEHYDROEPIANDROSTERONE (DHEA)

Dehydroepiandrosterone (DHEA) is an adrenocortical steroid that exhibits a physiological decline in circulating levels with age. Rose and colleagues found significantly decreased plasma DHEA levels in breast cancer patients compared to age-matched controls, suggesting a protective effect of DHEA against breast carcinogenesis.[49] In fact, a study from the National Cancer Institute at Frederick, MD demonstrated that supplementation of rats with DHEA was associated with the inhibition of xenobiotic-mediated CYP1B1 induction and carcinogen activation.[50] DHEA supplementation is therefore putatively chemopreventive in carriers of rapid-metabolizer CYP1B1 SNPs. Importantly, DHEA can be metabolized to estrogen thereby increasing the overall amount of the hormone. Therefore it is important that this intervention be used only in patients who have the CYP1B1 SNP.

S-ADENOSYLMETHIONINE (SAM)

In-vitro experiments by Werner and colleagues have demonstrated the ability of S-adenosylmethionine (SAM) to ameliorate the toxicity of catechol compounds (such as 4-OHE_2) to human neurons by acting as a co-substrate for COMT during catechol methylation reactions.[51] SAM supplementation is therefore potentially protective in COMT slow-metabolizers.

DIETARY ANTIOXIDANTS

A meta-analysis of 15,320 breast cancer cases from the Nanjing Medical University in China reported a significant interaction between a SNP in MnSOD and low antioxidant consumption in association with breast cancer.[52] Dietary antioxidants are postulated to reduce the burden of oxidative stress detoxification by the enzymes COMT, GST, and MnSOD.

Regardless of previous estrogen exposure, breast cancer status or estrogen metabolism profile, clinicians can help women prevent breast cancer through targeted interventions and ongoing monitoring.

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