Genetic Lifehacks
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Estrogen Metabolism

How It Is Made and How We Get Rid of It

Estrogen Creation and Metabolism

Types of Estrogen

- **Estradiol (E2)**: Primary form in women before menopause.
- **Estrone (E1)**: Primary form post-menopause and in men.
- **Estriol (E3)**: Main type during pregnancy.
- **Estetrol (E4)**: Produced by the fetus during pregnancy.

Estrogen Receptors

There are several different estrogen receptors:

- **ERα receptor** is encoded by the gene **ESR1** gene.
- **ERβ** receptor is encoded by the **ESR2** gene.
- **GPER1** (G protein-coupled estrogen receptor 1) is encoded by the GPER1 gene.

BPA, Phthalate

Binds to estrogen receptors, increasing risk of conditions like endometriosis, breast cancer.

Genes Involved in Estrogen Metabolism

Phase I: CYP1B1, CYP1A1, CYP1A2 enzymes produce catechol estrogen metabolites (2-OHE1, 4-OHE1, 16α-OHE1).

Phase II: COMT, UGT genes convert metabolites to water-soluble forms for excretion.

Cancer Risk Metabolites

Breast Cancer: Increased risk with 4-OHE1, 16α-OHE1; decreased risk with higher 2-OHE1:4-OHE1 ratio.

Prostate Cancer: Increased risk with 4-HOE1.

Estrogen Balance

- **Diindolylmethane (DIM) Supplements:** Increase beneficial estrogen metabolites.
- **Diet:** Cruciferous vegetables rich in DIM.
- **Calcium D-Glucarate:** Enhances elimination of estrogen metabolites.

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Estrogen Creation and Metabolism

(Article: https://www.geneticlifehacks.com/estrogen-how-it-is-made-and-how-we-get-rid-of-it/)

Estrogen is a steroid hormone that is synthesized from cholesterol and is important in reproduction, bone density, heart health, and brain health.

There are several different types of estrogen, and it is a hormone important in both males and females, although at different levels. Estrogen – from how much is made to how it is broken down – is dependent on both genetics and lifestyle factors affecting both men and women.

Let's get started by looking at the types of estrogen and how it is created, including the genes involved. Then we will dive into the research on estrogen metabolites and how they can affect your health. Genetic variants in the estrogen metabolism genes can affect cancer risk and your body's tolerance for estrogen-mimicking chemicals.

Types of estrogen:

There are several forms of estrogen in the body, and the amounts of each type become important for hormone-related cancer risk and uterine fibroids.[ref]

- **Estradiol (E2)** or 17β-Estradiol – the primary form in women before menopause
- **Estrone (E1)** -primarily made after menopause, primary form in men
- **Estriol (E3)** – the main type of estrogen during pregnancy
- **Estretrol (E4)** – only during pregnancy, made by the fetus

For the most part, we will focus here on estradiol (E2) and estriol. In addition to these types of estrogen, there are also estrogen metabolites created from the breakdown of estrogen, which we will cover below.

How is estrogen created in the body?

Estrogen is synthesized in the following tissues:[ref]

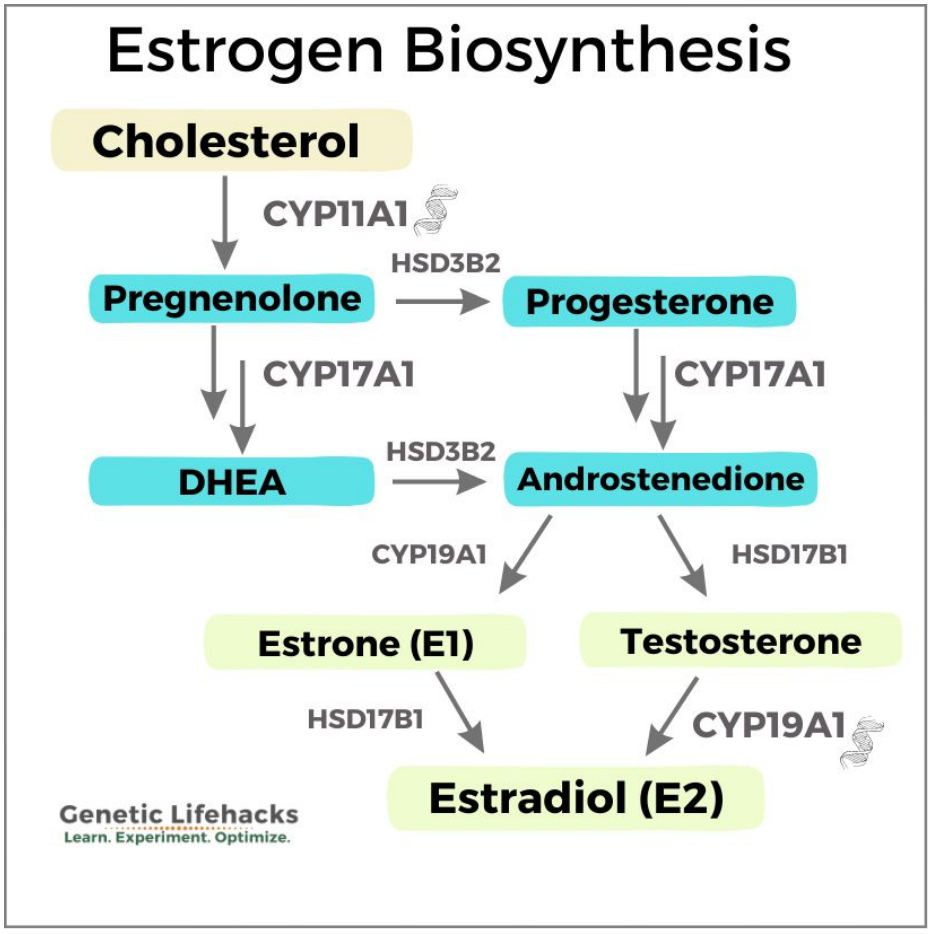
- ovaries (major source in women, E2)
- testes (males)
- fat cells (E1, especially post-menopause)
- brain
- liver
- pancreas
- intestines
- adrenals

The precursor for estrogen is cholesterol, which is first converted (using CYP11A1) into progesterone, which is then converted (using CYP17A1) into androstenedione.

Androstenedione can be converted into testosterone, dihydrotestosterone, or estrogen.

If it goes the estrogen route, androstenedione is converted (using CYP19A1) first to estrone (E1), which is then converted (using 17β-HSD) into estradiol.[ref]

Here is a flow chart to give you a better idea of the conversion of cholesterol into estrogen, including the genes that are involved.



Estrogen Sulfate: Storage form of estrogen

On a hormone lab panel test, you will likely see estrogen sulfate listed. Estrogen sulfate is the most abundant form of estrogen, but it is also not very active. It can be considered as a storage form of estrogen that can be converted by HSD17B1 (17β-Hydroxysteroid dehydrogenase) into estradiol. High levels of estrogen sulfate can be a risk factor for breast cancer.

Driving estrogen production: FSH

Within follicle cells in the ovary, the conversion of the steroid hormone precursor

into estrogen is controlled by follicle-stimulating hormone (FSH) levels. FSH is produced in the pituitary gland, and, along with luteinizing hormone (LH), controls the menstrual cycle.

Estrogen Receptors: Controlling Genes

So what exactly does estrogen do in cells?
Estrogen is transported throughout the body and can bind to estrogen receptors in the cell nucleus controlling the transcription of many different genes. Thus, the different estrogen receptors can control whether a gene gets transcribed into a protein that is used in the cell.

There are several different estrogen receptors:

- **ERα receptor** is encoded by the gene **ESR1** gene.
- **ERβ** receptor is encoded by the **ESR2** gene.
- **GPER1** (G protein-coupled estrogen receptor 1) is encoded by the GPER1 gene.

The estrogen receptors can bind to and **turn on hundreds of different genes.** Some important targets of estrogen include the LDL receptor, progesterone receptor, IGF-1, and many more. These genes are related to **hormones, cholesterol, and growth** within the body.[ref]

Estrogen receptors (ERs) are present in a wide variety of tissues in the body. For example, ERs are important in vascular endothelial cells, which line blood vessels. Estrogen receptors are found in cardiomyocytes (heart muscle cells), neurons, airway cells, muscles, the uterus, testes, fat tissue, bone, breast, kidneys, and more.

Estrogen receptors can also cause rapid activation of signaling pathways, or immediate changes, in certain cells. Estrogen can also impact mitochondrial biogenesis, function, and regulation of ATP production.[ref]

In a nutshell, estrogen causes the body to increase the production of other hormones, growth factors, and metabolic factors.

What does estrogen do in the body?

For women, estrogen regulates the **menstrual cycle** and is imperative for **reproduction**. The primary and secondary sexual characteristics of women (breasts, wider hips, lack of facial hair, etc) are due to estrogen production starting in puberty.

For **men and women,** estrogen is also important in maintaining **bone density and cognitive function.** Low estrogen is linked to osteoporosis. It is also important in brain function and controlling inflammation.[ref]

In men, estrogen is also necessary at low levels in the **production of sperm**. The loss of the estrogen receptor in the testes results in abnormal sperm. On the other hand, too much estrogen can also be detrimental to male reproductive health.[ref] Balance is key.

What happens when you have too much estrogen?

Signs of excess estrogen **in women** include:

- weight gain
- heavy periods
- fibroids
- PMS
- fibrocystic breasts
- loss of sex drive
- fatigue, depression, anxiety

For **men**, too much estrogen leads to:

- gynecomastia
- sexual dysfunction
- loss of muscle mass
- fatigue, depression, anxiety

Outside of estrogen's essential role in reproduction, estrogen plays a key role in the control of energy metabolism.[ref]

Getting rid of estrogen (metabolism or breakdown and elimination):

The level of estrogen in the body needs to be at the right level for the individual's age and sex. To control the level of estrogen in the body, we have to have multiple ways to break it down and eliminate it. This is a multi-step process involving what are known as phase I and phase II detoxification enzymes.

Phase I and Phase II estrogen metabolism:

In the liver, the CYP450 enzymes can metabolize estrogen. Specifically, this is done by the **CYP1B1, CYP1A1, or CYP1A2** enzymes.

This process creates metabolites known as 2-OHE1 (E2), 4-OHE1(E2), and 16α-OHE1, all of which are also known as **catechol estrogen metabolites**.

These catechol estrogen metabolites can be further changed by the **COMT** (catechol-O-methyltransferase) enzyme or through glucuronidation (**UGT** genes) This makes them water-soluble and able to be excreted through urine or feces.[ref]

Essentially, this two-step process needs to work in tandem:

- Phase I: the CYP1B1 or CYP1A1 enzyme breaks down estradiol into the catechol estrogen metabolites.
- Phase II: they need to be made into water-soluble substances (by COMT, UGTs).

It is important that the two phases of estrogen metabolism act in sync.

Some of the metabolites, such as 16α-OHE1, are also able to activate the estrogen receptors. These specific estrogen metabolites increase the risk of breast cancer.[ref] Thus, you don't want certain Phase I metabolites hanging around in the body.

Estrogen metabolites linked to breast, ovarian, and prostate cancer:

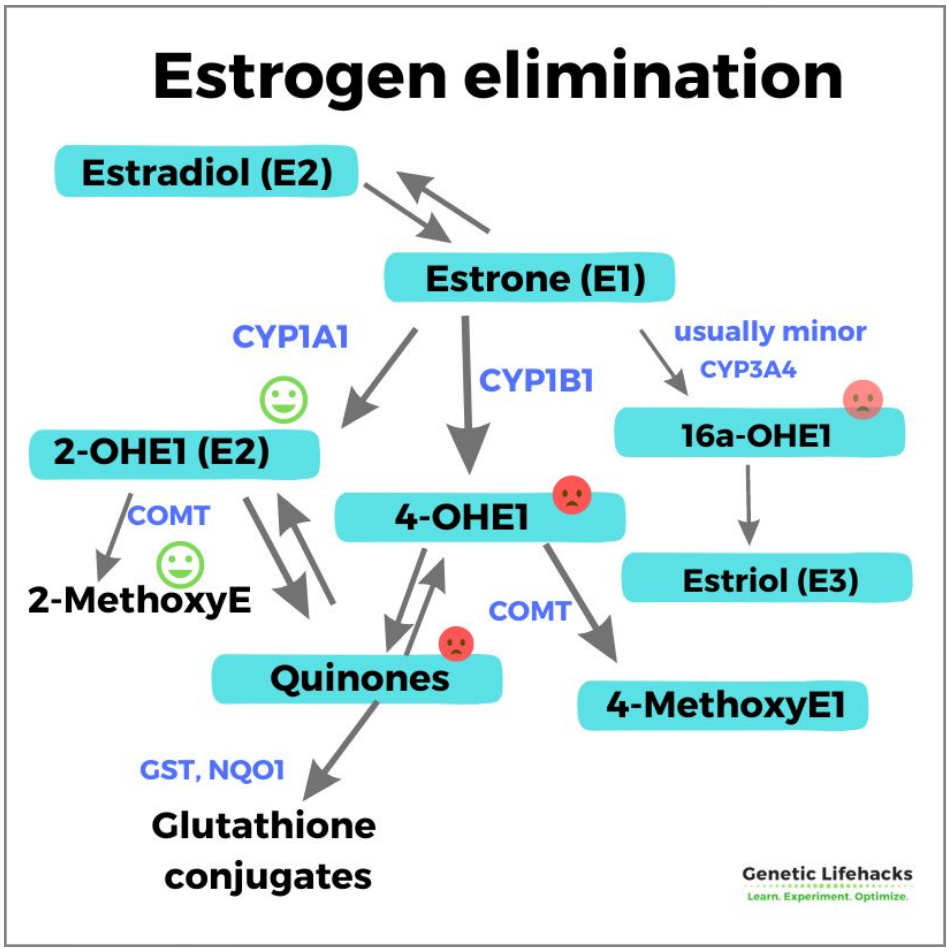
For **breast cancer**, the **4-OHE1(E2) and 16α-OHE1** metabolites are implicated in increasing the relative risk of cancer.

Higher amounts of 2-OHE1(E2) or a better ratio of 2-OHE1:4-OHE1 decreases breast cancer risk. Additionally, you don't want too much estrogen (E1 or E2), in general, hanging around. Everything needs to be in balance.[ref][ref]

Prostate cancer risk is increased with **4-HOE1(E2)** metabolites also.[ref]

In general – the estrogen metabolites that start with "2" are good and the ones that start with "4" or "16" need to be limited or at least eliminated quickly from the body.[ref]

Here is a diagram of how these metabolites go together:



As you can see, upregulating the CYP1A1 enzyme is going to increase the 2-OHE1 path.

Too much estrogen being metabolized through CYP1B1 into 4-OHE1(E2) and the estrogen quinones can potentially be bad if your body has slower phase II (COMT, GSTP1, GSTM1, NQO1) enzymes.[ref][ref]

The connection between smoking and estrogen-related cancers:

Smoking significantly increases the risk of breast cancer and prostate cancer.

Part of the smoking increases cancer risk in general is that it can cause DNA damage. However, smoking specifically increases the risk of breast cancer

through upregulating the CYP1B1 and CYP1A1 enzymes. For people with genetic variants that cause more of an impact on CYP1B1 upregulation – combined with an inability to eliminate the estrogen metabolites fast enough (due to phase II genes, diet, and lifestyle) – then cigarette smoking is going to significantly increase the 'bad' estrogen metabolites. Smoking also may impair the phase II metabolites, thus creating more estrogen quinone metabolites with a decreased ability to eliminate them.[ref][ref]

Therefore, combining some of phase I and phase II genetic variants (see the genotype report below) with smoking causes a fairly large increase in the risk of cervical, breast, or prostate cancer.

Estrogen Elimination: Phase III

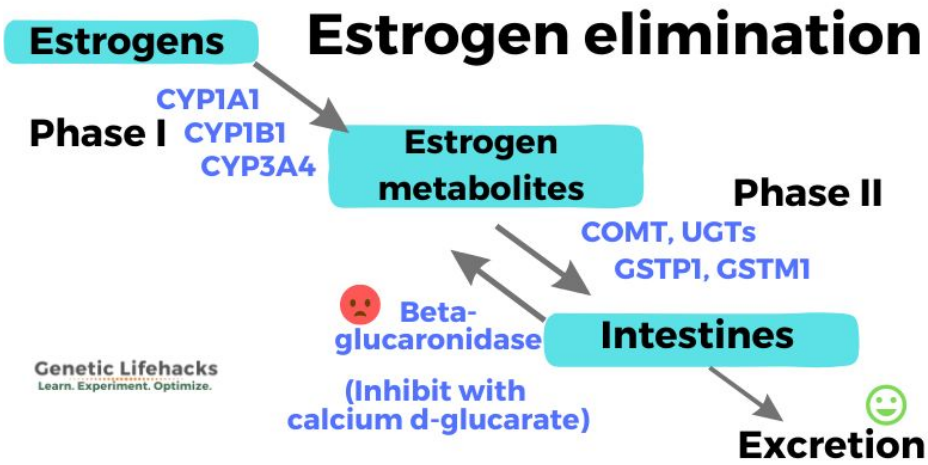
Let's go one step further and make the two-step process of estrogen metabolism into a three-step process…

Once the catechol estrogen metabolites have been metabolized (COMT), they have to be excreted (urine or feces).

The gut microbiome comes into play here in making sure that the metabolites are excreted and not reabsorbed. The estrogen that has been metabolized and is ready to be eliminated through feces can actually be recycled back into circulation due to an interaction with certain bacteria in your gut microbiome.

Beta-glucuronidase, an enzyme produced by the gut microbiome, can reverse the reaction that the UGT enzymes did to make the estrogen metabolites more water-soluble. This can cause the estrogen metabolites to be reabsorbed from the intestines and go back into circulation.[ref]

Calcium D-glucarate can suppress the beta-glucuronidase activity in the gut, thus increasing the number of estrogen metabolites that are excreted.[ref]



Estrogen Mimics: BPA, Phthalates, and Other Toxicants

There are several environmental toxicants that act similarly to estrogen in the body. Among these, phthalates and BPA are ubiquitous, with research showing that almost everyone has them in their bodies. These estrogen-mimicking chemicals can bind to the estrogen receptors, similarly to the way that estrogen binds.[ref][ref]

Phthalates are used in vinyl, plastics, adhesives, artificial fragrances (laundry detergent, air freshener), personal care products, and more.[ref]

BPA is also found in plastics, and we are exposed through food and drinks being stored in plastic containers or cans with linings containing BPA. Even the paperboard used in food packaging (especially if it is recycled cardboard) can contain BPA, which is then transferred to the food we eat.[ref]

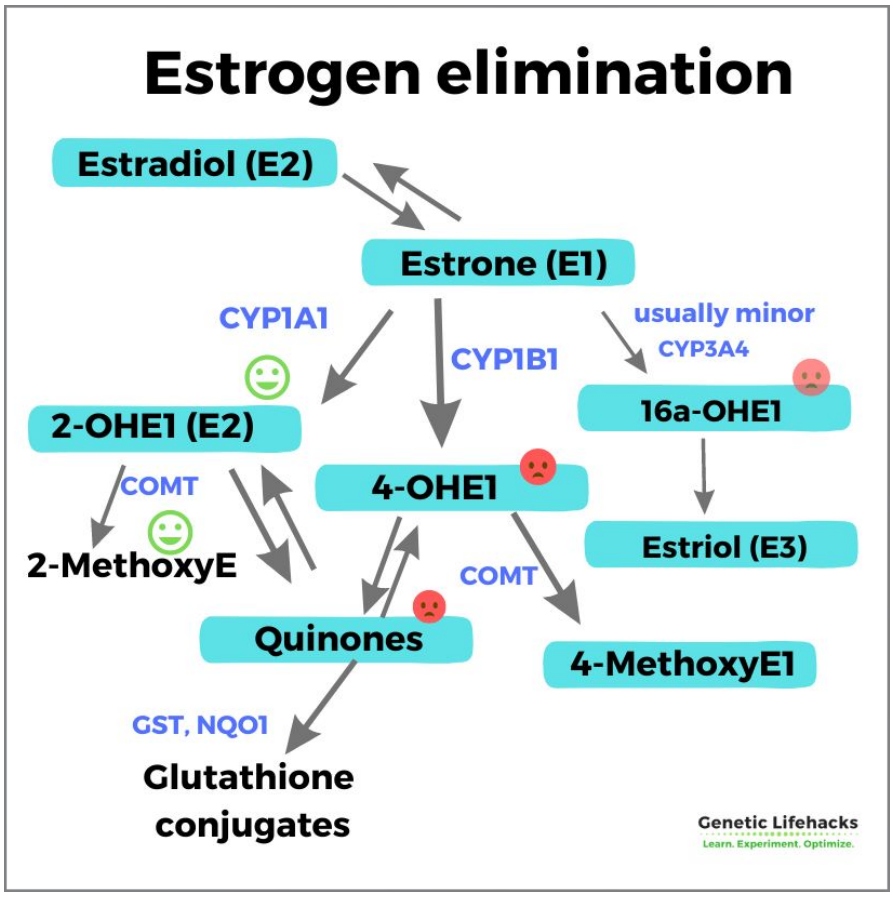
These estrogen mimics (at the levels found in people every day) have been linked to increased risk of several estrogen-related conditions, including:

- endometriosis[ref]
- enlarged prostate[ref]

- almost 2-fold increase in breast cancer for higher phthalate exposure (estrogen receptor-positive)[ref]
- BPA exposure at low levels is linked to increased breast and prostate cancer[ref]
- uterine fibroids[ref][ref]

We will cover more on how to avoid and eliminate these estrogen mimics in the Lifehacks section. First, though, let's cover how your genes interact with estrogen metabolism (phase I and phase II) and how your genes impact estrogen creation.

For your reference, here is the overview of estrogen elimination:



Genotype Report

(Note that the full article includes the genotypes for individual variants.)

Phase 1 metabolism of estrogen:

CYP1A1 gene: The CYP1A1 enzyme is involved in phase I detoxification of estrogen into 2-OHE1(E2). CYP1a1 is also used to metabolize polyaromatic hydrocarbons, such as from cigarette smoke, and arachidonic cid.

CYP1B1 gene: encodes an enzyme utilized in the phase I detoxification of estrogen into 4-OHE1(E2)

CYP3A4 gene: encodes an enzyme that converts estrogen into 16a-OHE1 (higher levels linked to breast cancer). This enzyme is also used in the metabolism of many prescription drugs.

Phase II estrogen metabolism genes:

COMT gene: encodes an enzyme needed for the phase II detoxification of estrogen metabolites.

GSTP1 gene: encodes glutathione S-transferase P1, a phase II detoxification enzyme important for reducing estrogen quinones. This enzyme is also used in other phase II detoxification reactions such as

GSTM1 gene: another phase II detoxification enzyme important for reducing estrogen quinones

UGT1A1/6 gene: phase II detoxification gene utilized in glucuronidation of estrogen metabolites

NQO1 gene: phase II detoxification enzyme

Genes involved in making estrogen:

CYP19A1 gene (aromatase): converts androstenedione and testosterone into estrogen

CYP17A1 gene: converts progesterone into androstenedione

HSD17B1 gene: encodes the enzyme that converts estrone to estradiol (E2)

Lifehacks for estrogen balance:

Testing is the only way to truly know your estrogen levels. You can order your own hormone test panels online (e.g. UltaLabs Estrogen Panel) or go through your doctor. A qualified professional can help you with making sense of your hormone test results.

The lifehacks below are based on natural supplements and lifestyle changes for reducing estrogen and shifting towards the less-risky estrogen metabolites. Please also talk with your doctor about prescription-based options and be sure to discuss any supplement interactions if you are on medications.

Optimizing Phase I detoxification for estrogen metabolism:

CYP1A1:
Diindolylmethane (DIM) is a compound found in cruciferous vegetables. DIM upregulates CYP1A1 while also acting on estrogen metabolism in other ways. [ref]

For someone who has a **slower CYP1A1 variant or a faster CYP1B1 variant**, this may be a good supplement to check out. DIM may also decrease CYP19A1 (aromatase), thus decreasing the production of estrogen to begin with.

Studies show DIM increases the ratio of 2-OHE1:16α-OHE1 — which may be beneficial for preventing cancer.[ref][ref] There is some good evidence it may be beneficial for prostate cancer as well[ref][ref], but not all studies agree[ref].

One way to increase DIM is to eat a lot of cruciferous vegetables. Cabbage is the cruciferous vegetable highest in DIM, while broccoli, Brussels sprouts, Turnips, and collard greens also contain DIM. DIM concentrations rise during cooking due to the activation of the myrosinase enzyme. Cooked cabbage, for example, has about 6-fold higher DIM concentrations than uncooked cabbage.[ref]

Can just eating more cabbage and broccoli prevent cancer? Research studies do show that women who eat the highest amounts of cabbage and broccoli reduce their relative risk of breast cancer by around 25-30%. In looking at several different studies, cabbage seems to have the most impact on breast cancer prevention.[ref]

Supplements containing DIM are also readily available at health food stores and online.

If you decide to supplement with DIM, a lot of clinicians recommend combining it with **calcium D-glucarate** (which helps with estrogen elimination). Jarrow sells a combo of DIM and calcium D-glucarate, or you can get them as separate supplements if you want to take them at different times of the day.

Timing of supplements:
The CYP1A1 enzyme levels rise and fall over a day along with the core circadian gene, CLOCK.[ref] Taking DIM in the morning may be more effective than taking DIM at night.

CYP3A4:
CYP3A4 is the enzyme needed for converting estradiol into 16α-OHE1, which is a metabolite of estrogen that is linked to an increased relative risk of breast cancer and prostate cancer.[ref]

Grapefruit juice and bergamot (both contain bergamottin) inhibit CYP3A4. It seems like inhibiting the production of 16α-OHE1 would decrease breast cancer risk, but inhibiting CYP3A4 may also increase the overall amount of estrogen in the body.

Studies on grapefruit and estrogen show mixed results: Drinking grapefruit juice lowers estradiol in postmenopausal women.[ref] One study did find eating grapefruit increased the risk of breast cancer a little bit.[ref] Another study found no effect from eating grapefruit.[ref] None of the studies looked at the ratio of 2-OHE1:16α-OHE1.

Just make sure that you don't drink grapefruit juice while taking a medication that needs the CYP3A4 enzyme. The effects of a 6 oz glass of grapefruit juice can last for 24 hours.[ref]

Piperine is a component of black pepper that also inhibits CYP3A4. Some studies show that piperine is beneficial in preventing breast cancer growth (in a lab setting).[ref] Note that piperine is sometimes included in supplements containing DIM.

St. John's wort increases CYP3A4.[ref][ref] I can't find any research studies, though, showing this could increase breast or prostate cancer risk. It may have benefits, such as inhibiting CYP1B1, that outweigh any possible negatives from the increase in CYP3A4.[ref]

Increasing Phase II enzymes:

You want to avoid 4-OHE1/2 hanging around, and if you have a slow COMT gene, the 4-OHE1 metabolites can be turned into estrogen quinones.

To get rid of the quinones, your body uses the phase II enzymes, GST's or NQO1. Both of which interact with Nrf2 and are increased by cruciferous vegetable intake. (Check your genetic variants for the Nrf2 pathway.)

Sulforaphane and/or cruciferous vegetable intake increase **GST and NQO1.** You can get sulforaphane from eating broccoli sprouts or via a supplement.

Cruciferous vegetables include **cabbage, broccoli, cauliflower, kale, collards, and Brussels sprouts.**

GSTP1 genotypes:
One study specifically found women with the GSTP1 rs1695 G/G genotype overall were at a slightly greater risk of breast cancer — but that was because cancer risk increased quite a bit when the women had a low **cruciferous vegetable** intake.[ref] Eating plenty of cruciferous vegetables should mitigate the risk of this variant.

NQO1 and Quinones:
N-acetyl cysteine (NAC) and resveratrol have been shown to reduce the catechol estrogen quinones (bad).[ref] These work by increasing the expression of NQO1, which reduces the quinones to catechols.[ref]

NAC and resveratrol are both available as supplements online and at your local health food store. (*Note that if you carry the NQO1 rs1800566 AA genotype which has very low enzyme activity, this may not be as effective for you*.)

Getting rid of estrogen mimics in your environment:

Both **phthalates and BPA** have been shown to mimic estrogen in the body and bind to the estrogen receptors.

The question of how to get rid of these ubiquitous chemicals is a tough one… Studies find that 90 – 100% of people have BPA and phthalates in their body on any given day.

Eliminating phthalates:
Personal care products that contain phthalates have been shown to significantly increase phthalate levels in the body. Go read the labels and see what you are using each day (shampoo, body wash, lotions, etc). Look for the long chemical words that contain 'phthalate' in them. For example, dibutyl phthalate or di-2-ethylhexyl phthalate.

Perfumes and artificial fragrances often contain phthalates.[ref] Cosmetics and perfume sales clerks were found to have higher phthalate levels after their shift at work.[ref] Synthetic air fresheners and laundry detergent fragrances can be another source.[ref]

A new study just came out this month showing skin exposure to phthalates from clothing is actually the largest source for babies (Chinese study).[ref] Other studies, though, point to inhaling phthalates through dust particles.[ref]

To sum up, for phthalates:

1. Avoid shampoo, lotions, and cosmetics that contain phthalates. Switch to more natural options.

2. Avoid artificial fragrances in air fresheners and laundry detergents. Essential oils provide a non-estrogenic alternative.
3. Wash new clothes before wearing to remove chemical residue, or consider purchasing used clothes.
4. Household dust is a major source of phthalate exposure from the breakdown of vinyl and furniture. Dust frequently and vacuum regularly.

Avoiding BPA:
BPA is well known for being found in plastics and plastic water bottles. However, other sources can also be significant routes of exposure. Many food packaging materials contain BPA. Canned foods have high levels of BPA due to the can linings containing PVC.[ref] BPA or BPS is also used on thermal cash register receipts.[ref][ref]

One study found using hand sanitizer and then holding a cash register receipt for a couple of minutes increased BPA levels considerably. This was done with people holding a cash register receipt after using hand sanitizer and then eating french fries. (This is such a real-world scenario for any germaphobe stopping for a fast-food lunch.) Wet hands were found to have a 100-fold increase in BPA transfer from the thermal printed receipt paper. There was also a huge increase in serum BPA (both transdermal and transfer to the french fries, although they only ate 10 french fries…).

To sum up, for BPA:

- Switching to eating fresh vegetables and cooking whole foods should help decrease BPA exposure from canned foods. A recent US population study found that BPA from food explains about 20% of daily exposure.[ref]
- Store your food in glass instead of plastic, especially if reheating in the microwave.
- Don't hold thermal printed receipts in a sweaty hand.
- As much as possible, choose beverages that are stored in glass instead of plastic.
- Avoid drinking hot beverages from plastic or disposable cups.

Limit Alcohol:

Alcohol consumption is linked to an increased risk of estrogen-related cancers. A 2006 study showed that premenopausal women who drank more than 25g/day of alcohol, which would be two beers or a large glass of wine, had a 40% increase in estrone (E1) levels.[ref] Chronic alcohol consumption also increases oxidative stress overall, which is going to indirectly affect phase II detoxification pathways. [ref]

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