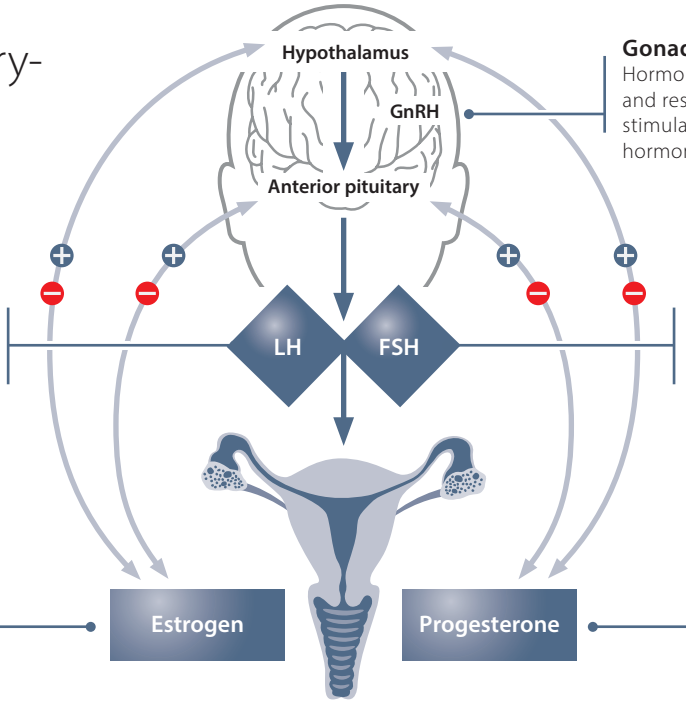
Estrogen metabolism

Estrogen affects the growth, differentiation, and function of numerous tissues throughout the female body—not just those involved in reproduction. This hormone plays an important role in bone health, protects the cardiovascular system, and influences behaviour and mood. While appropriate levels of estrogens are essential for good health, several studies conclude inappropriate, and increased, exposure to estrogen leads to elevated risk for several types of cancers including those affecting breast, ovaries and thyroid. Furthermore, disproportionate estrogen exposure can play a role in other female-related health problems including polycystic ovarian syndrome (PCOS), premenstrual syndrome (PMS), endometriosis, and fibrocystic or painful breasts (mastalgia).

Various lifestyle and environmental factors can influence estrogen production, metabolism, and balance. These include poor diet, obesity, excess alcohol consumption, high insulin levels, medications such as those used for hormone replacement therapy, contraceptive pills and over exposure to chemicals used in pesticides and other industrial compounds. Estrogen levels have also been found to be affected downstream by agricultural hormones found in animal products that are subsequently consumed by humans. Genetics can also play an important role in determining estrogen levels.

Hypothalamic-pituitary-gonadal (HPG) axis



Gonadotropin-releasing hormone (GnRH)
Hormone released through the anterior pituitary and responsible for the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

Luteinizing hormone (LH)
Works with follicle-stimulating hormone (FSH) to stimulate the release of the egg from the ovary (ovulation). LH is controlled by the hypothalamus and pituitary gland.

Follicle-stimulating hormone (FSH)
Acts in conjunction with luteinizing hormone (LH) to stimulate release of eggs by ovaries (ovulation). It is controlled by the hypothalamus and pituitary gland.

Estrogen
A hormone that plays a role in many aspects of a woman's health throughout her lifespan including libido, mood, joint health, and cognition. Estrogen is secreted from the ovary by the developing egg cells to signal to the endometrial lining of the uterus to develop and prepare for possible embryo attachment.

Progesterone
The interplay between estrogen and progesterone from the ovaries regulate the normal menstrual cycle. Progesterone is secreted by the ovary after ovulation and has local effects in the uterus as well as systemic effects on mood, libido, and counters some of the potential negative effects of estrogen. In times of stress an increased amount of progesterone and its precursor pregnenolone may be used to make the stress hormone cortisol, which may impact overall sex hormone production as both estrogen and testosterone are made from progesterone.

Hormone test considerations

- Estrogen dysregulation occurs when estradiol and progesterone levels are in an unbalanced or inappropriate ratio outside of normal reference ranges.
- Labs to consider are urine, blood, and saliva.
- Genomic testing may be addedfor a more comprehensive evaluation.

Hormone feedback control:
Estrogen and progesterone exert feedback control on the hypothalamus and anterior pituitary gland, helping control the release of GnRH, LH, and FSH.

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Genetic Potential Through Nutrition

Potential Causes and Symptoms of Estrogen Dysregulation

Causes

Perimenopause
Women experiencing perimenopause may show higher levels of estrogen relative to progesterone during the initial phase.

High cortisol levels
High levels of cortisol can block progesterone receptors, leading to an imbalanced estrogen to progesterone ratio.

Xenoestrogens
Synthetic chemicals can mimic effects of estrogen and are also known as endocrine disruptors. These include BPA, phthalates, parabens, and other industrial chemicals.

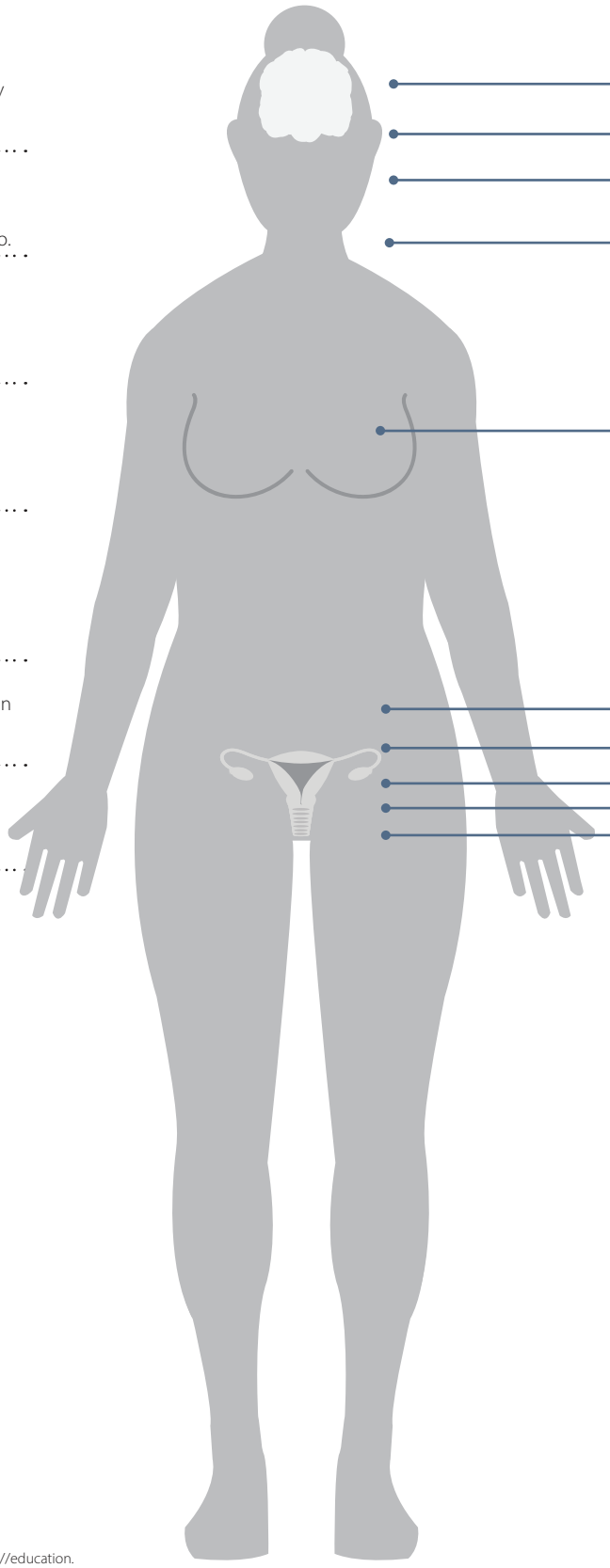
Obesity & weight gain
Fat cells produce more estrogen, while obesity lowers sex hormone-binding globulin (SHBG), leading to the increase of free estrogen in the blood.

Diet & alcohol
A diet high in conventionally raised red meat and refined carbohydrates may lead to increased levels of estrogen. Excess consumption of alcohol can also raise estrogen levels.

Nutritional deficiencies
Specific deficiencies of magnesium, vitamin B_{12}, folate, zinc, and copper can lead to increased levels of estrogen.

Heavy metals
Heavy metals including mercury act as xenoestrogens by binding to estrogen receptors.

Symptoms



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The ultimate biologic effect of estrogen depends on how it is metabolised. The metabolism of estrogen takes place primarily in the liver through Phase I (hydroxylation) and Phase II (methylation and glucuronidation) pathways, which allow estrogen to be detoxified and excreted from the body. Hydroxylation yields three estrogen metabolites that vary greatly in biological activity: 2-hydroxyestrone (2-OH), 16-hydroxyestrone (16α-OH), and 4-hydroxyestrone (4-OH).[14] The 2-OH metabolite is generally termed the "good" estrogen because it generates very weak—and therefore potentially less harmful—estrogenic activity in the body. In contrast, the 16α-OH and 4-OH metabolites show persistent estrogenic activity and may promote dangerous tissue growth if unchecked.[16] In fact, women who metabolise a larger proportion of their estrogen via the 16α-OH metabolite may be at significantly higher risk of developing breast cancer.[17]

The 2-OH and 4-OH estrogen metabolites are further detoxified via a process called methylation. This is an important pathway, because it renders the harmful 4-OH metabolite significantly less active and also activates the protective 2-OH into the beneficial (and more active) 2-methoxyestrone (2-MeOE1 & 2). Furthermore, if the 2-OH and 4-OH estrogens are not methylated, they can be converted to highly reactive molecules that could potentially damage DNA.[16-18] Glucuronidation is one of the key Phase II liver detoxification pathways for estrogen, facilitating its elimination from the body.[19]

Mechanism of action

"Estrogen" is a term that is used to collectively describe the female hormones estradiol, estrone, and estriol. The most potent of these is estradiol. Estrogens circulate in the body mainly bound to the sex hormone-binding globulin (SHBG), and only unbound estrogens can enter cells and cause biological effects.[14-15] Therefore, any change in the concentration of SHBG will alter estrogen activity by changing the availability of estrogen to the target cell.

Nutrients a mechanism of action

There are several pathways in the estrogen metabolism cascade where certain nutrients and bioactives have been studied for their influence on the mechanism of action, either in humans or in preclinical studies. These mechanisms of action and the nutrients that have been studied are referenced in the table below:

Nutrients and Bioactives	Mechanism of Action
Cruciferous vegetables, indole-3-carbinol, 3,3'-diindolylmethane (DIM), xanthohumol, rosemary, isoflavones (soy, kudzu, clover)[20-25]	Promote C-2 hydroxylation over C-4 and/or C-16α hydroxylation of estrogens
Vitamins A, E, & C, N-acetylcysteine, superoxide dismutase (SOD), turmeric, green tea, lycopene, α-lipoic acid, flavonoids[26-30]	Reduce the oxidation of catechol estrogens (2-OH and 4-OH)
Folate; vitamins B_2, B_6, & B_{12}; trimethylglycine; magnesium[31-32]	Promote the methylation of catechol estrogens (2-OH and 4-OH)
Fibre, lignans (flaxseed), isoflavones (soy, kudzu, clover)[33-37]	Increase circulating concentrations of SHBG, thus reducing levels of unbound, active estrogens
Lignans (flaxseed), flavonoids (chrysin)[38-40]	Inhibit the activity of aromatase, which converts androgens into estrogens
Turmeric or curcumin; milk thistle; D-limonene; magnesium; vitamins B_2, B_6, & B_{12}; flavonoids[19, 30, 41]	Promote the detoxification of estrogens by upregulating Phase I and Phase II enzymes
Fibre, probiotics (*L. acidophilus* NCFM®, Bifidobacteria), calcium D-glucarate[42-45]	Inhibit the activity of β-glucuronidase, which deconjugates estrogens in the large intestine, allowing them to bereabsorbed and their estrogenic activity to continue
Isoflavones (soy, kudzu), lignans (flaxseed), indole-3-carbinol, DIM, xanthohumol, resveratrol[46-52]	Modify estrogen receptor activity

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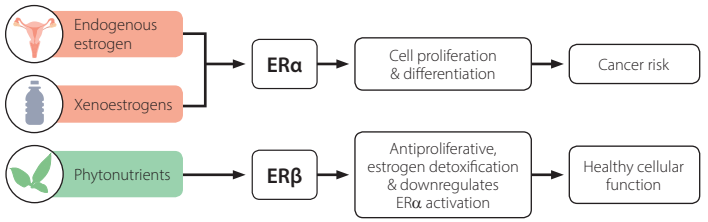
Estrogen metabolism and nutritional influences

Estrogen is the primary hormone responsible for sexual and reproductive development in women. Once puberty begins, the body uses estrogen to regulate the first half of the menstrual cycle and then metabolises the hormone for elimination via urination and defecation. Dietary and lifestyle modifications that support a healthy weight, like consuming a nutrient-dense dietary pattern (e.g., increasing intake of fibre and phytoestrogens) and being physically active, have been linked to the modulation of estrogen metabolism. In addition, many nutrients and nutritional bioactives have been studied for their influence on pathways of estrogen metabolism and detoxification, including but not limited to isoflavones, indole-3-carbinol, B vitamins, magnesium, limonene, calcium D-glucarate, and antioxidants. Methylated folate and B12, along with vitamins B2 and B6, provide critical methyl groups and act as co-factors that fuel the COMT activated methylation cycles which transform hydoxylated estrogen metabolites into less harmful molecules which can safely be eliminated.

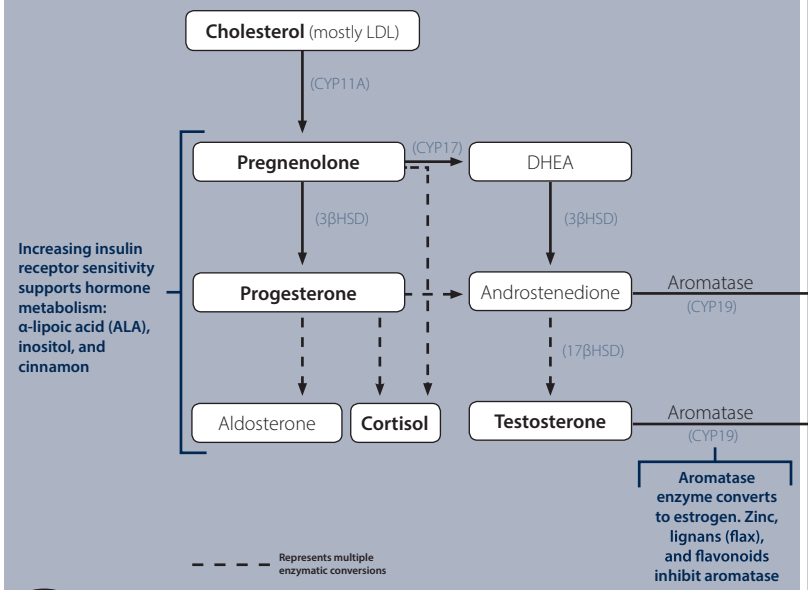
Estrogens & estrogen receptor sensitivity

Estrogen receptors (ER) are present in both men and women. Endogenous estrogens, environmental xenoestrogens, and their metabolites selectively bind to estrogen receptors. Various phytonutrients, such as phytoestrogens, may moderate their binding, modulating cell signaling to support hormone balance.

Phytoestrogen (plant-derived estrogens) examples include lignans, isoflavones (genistein, daidzein), and resveratrol. Vitamin B_6 helps modulate tissue response.

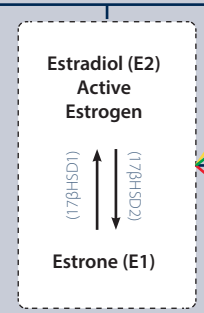


Production and conversion of estrogen

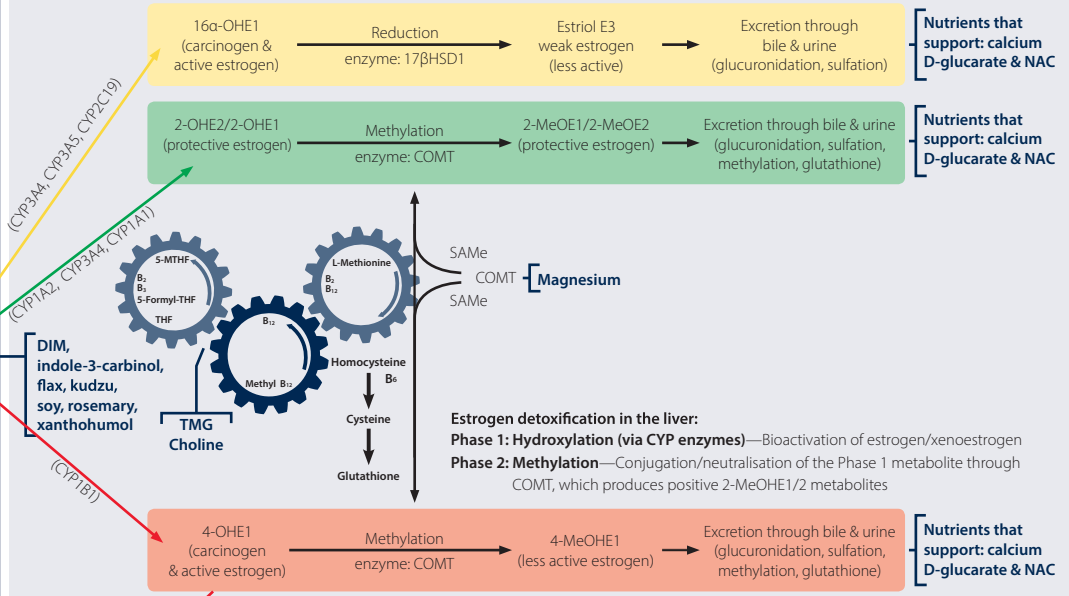


The body's systemic pool of estrogen

Lignans (found in fiber-rich foods) & isoflavones (found in legumes) help regulate production of sex hormone-binding globulin (SHBG), which assists in the regulation of free estrogens, testosterone, and dihydrotestosterone in circulation



Estrogen detoxification: bioactivation, conjugation, and elimination



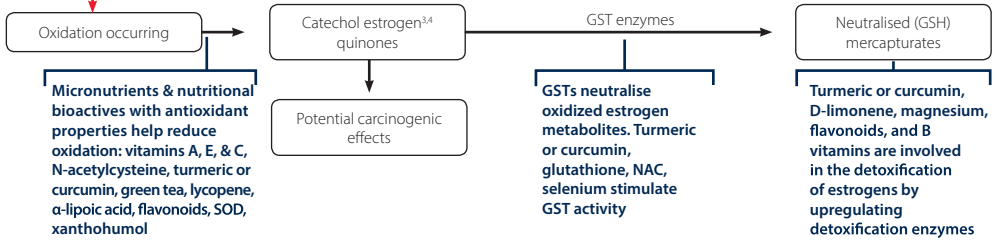
Estrobolome—gut & estrogen connection

The gut plays a vital role in the body's ability to clear unwanted estrogen metabolites. Gut dysbiosis can contribute to β-glucuronidase activity, which allows estrogen to re-enter circulation and increase the estrogen pool. Effects can be unbalanced hormones. Proper gut health, nutrition, and the types and amounts of macronutrients support estrogen biotransformation and clearance.

- **5R gut protocol, probiotics, prebiotics, fiber (apple pectin)**
- **β-glucuronidase inhibitors: probiotic strain *L. acidophilus* NCFM®, calcium D-glucarate; lignans**
- **Flax lignans support excretion**

Liver & estrogen detoxification

Balancing Phase I and Phase II enzyme systems in the liver supports healthy estrogen detoxification and encourages the clearance of genotoxic 4-OHE1 metabolites through the induction of Nrf2, quinone reductase (NQO1), GSTs,* and GSH.



KEY: CLA: conjugated linoleic acid; **COMT:** catechol-O-methyltransferase; **DHEA:** dehydroepiandrosterone; **5-formyl-THF:** 5-formyltetrahydrofolate; **HRT:** hormone replacement therapy; **5-MTHF:** 5-methyltetrahydrofolate; **NAC:** N-acetylcysteine; **SAMe:** S-adenosylmethionine; **SAH:** S-adenosylhomocysteine; **SHBG:** sex hormone-binding globulin; **THF:** tetrahydrofolate; **TMG:** trimethylglycine; **Nrf2:** nuclear factor erythroid 2 (NF-E2) p45-related factor 2; **NQO1:** NAD(P)Hquinone oxidoreductase 1; **GST:** glutathione S-transferase; **GSH:** reduced glutathione; **2-OHE1:** 2-hydroxyestrone; **2-OHE2:** 2–hydroxyestradiol; **2-MeOE1:** 2–methoxyestrone; **2-MeOE2:** 2-methoxyestradiol; **4-OHE1:** 4-hydroxyestrone; **4-MeOHE1:** 4-methoxyestrone; **16α-OHE1:** 16α-hydroxyestrone

*GSTs: glutathione S-transferases are important enzymes of detoxification and intra-cellular binding proteins