SIDE *effects*

Many of the side effects from ET are caused by a reduction in oestrogen levels and the subsequently lower amount of oestrogen to act on normal cells in the body – these symptoms are called menopausal symptoms. Tamoxifen can also cause very specific side effects- see below. Oestrogen is a 'vitality' hormone and by lowering its levels in the body, some side effects can occur as follows:

- **Hot flashes and night sweats** – this result from less oestrogen to stabilise the muscles around your blood vessels. Typically a woman will experience redness and the feeling of heat in the chest and face. Sweating can also occur. In some women, this is worse at night time
- **Joint/muscle aches and pains (also known as arthralgia/myalgia)**
- **Vaginal dryness**
- **Reduced libido**
- **Reduced energy**
- **Memory impairment**
- **Interferes with normal sleeping**
- **Osteoporosis** – oestrogen works to reduce bone degeneration or bone loss. A reduction of oestrogen can reduce the density of your bones and increase the risk of fracture, especially in the setting of minimal trauma. It is important to know that Tamoxifen does not have a "bone losing effect" and can in fact improve bone mineral density. You will have your bone mineral density checked at the beginning of and during (every 1-2 years) your ET. If you do develop osteoporosis or have a fracture, medications to increase bone mineral density can be started. It is usually recommended to take Vitamin D and Calcium supplementation as well as having a balanced diet and include regular weight bearing exercise to prevent these complications.
- **Heart disease** – including coronary artery disease and heart attack. The mechanism relating heart problems with ET (particularly aromatase inhibitors) is not well understood. The risk of heart disease as a result of ET is less than 1%. There are ways to reduce this risk including maintaining a healthy weight with a balanced diet and exercise, as well as monitoring other risk factors such as blood pressure, lipid profile and diabetes with your family doctor.

You should talk to your oncologist if you develop any of these side effects. There are several well-researched strategies to manage these symptoms.

TAMOXIFEN SIDE EFFECTS

In addition to the side effects mentioned above, there are some special considerations with tamoxifen.

- **Blood clot in the veins** – small risk (approximately 1-2%) in the calf muscle or in the lungs whilst on tamoxifen. There is no need to take blood thinners. If you are sitting for prolonged periods (e.g. long flight or car journey for several hours) or in need of surgery which will require you to be in a hospital for several days, please let your oncologist or surgeon know and they will advise if you need to stop tamoxifen for a short period of time.
- **Uterine cancer** – this is a very uncommon side effect of tamoxifen therapy occurring in less than 1% of women on this treatment. The risk is higher with increasing age. If you develop any vaginal bleeding, spotting or pelvic pain whilst taking tamoxifen, you must inform your family doctor or oncologist. You may then need to see a gynaecologist for a hysteroscopy (a procedure which examines the inside of your uterus).
- **Retinal (i.e. back of your eye) disease** – tamoxifen can cause crystal-like deposits on the back of the eye, affecting vision. This is a very rare side effect. This side effect is generally seen only in patients taking high doses of Tamoxifen, not the smaller dose for cancer treatment. Alert your specialist if you develop a reduction in your vision or visual changes.
- **Vaginal secretions** – Tamoxifen can cause increased vaginal secretion instead of vaginal dryness.

FULVESTRANT SIDE EFFECTS

- Mild discomfort at the site of the injection

HOW LONG WILL I BE ON *Endocrine Therapy?*

Early breast cancer (after surgery) – the role of ET after breast cancer surgery is to reduce the risk of breast cancer recurring. Patients will be on endocrine therapy for a minimum of five years after surgery (and/or chemotherapy). Some patients will benefit from extending this treatment up to ten years. It may involve switching ET or staying on the same therapy for 10 years.

Advanced or Metastatic Breast Cancer – ET is used to control or kill breast cancer growth. It is often used in combination with other therapies that suppress cancer growth. ET will be given for as long as it is effective in controlling your breast cancer and your oncologist will help you with side effects, so please discuss this with him or her.

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ENDOCRINE THERAPY *in Breast Cancer*

WHAT *is it?*

Endocrine therapy (ET) is the kind of treatment that reduces the production of female hormone, oestrogen, or blocks oestrogen from stimulating any potential cancer cells in your body. It is an important component of breast cancer treatment. ET is only used in patients who have oestrogen (ER) and/or progesterone receptors (PR) detected in their breast cancer, also known as ER/ PR positive breast cancer.

WHAT DOES *oestrogen do?*

Oestrogen (or estrogen) is a sex hormone which is responsible for growth and various organ maturation throughout your life and has important functions in both women and men. It plays an important role in sexual organ maturation at different stages of life, for instance at puberty, menstruation, pregnancy, breast and milk duct development, and also in bone and heart health.

HOW IS OESTROGEN FORMED *in the body?*

- **Before menopause** – oestrogen is produced by the ovaries. As shown in **Figure 1**, the ovaries are stimulated by the hormones secreted from a gland in the brain.

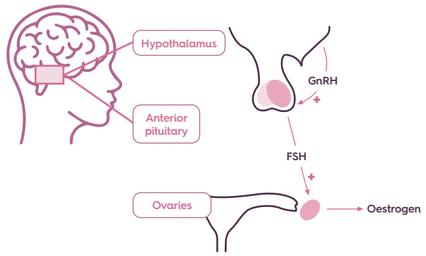


Figure 1. *the hypothalamus in the brain secretes a hormone called GnRH which stimulates another gland in the brain to produce a hormone called FSH. FSH is released into the blood and stimulates the ovaries to produce oestrogen. Oestrogen is then released into the blood stream to take effect on various cells in the body.*

- **After menopause or in men** – When ovaries stop producing oestrogen (that is a woman goes into menopause – usually as a woman gets older or because the ovaries have been removed), oestrogen can be produced in the organs in the body in very low quantities. This latter process of oestrogen production is similar in men.

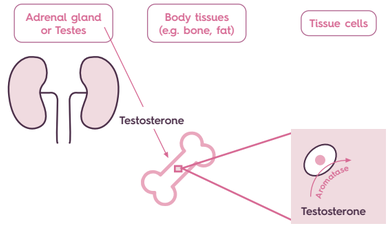
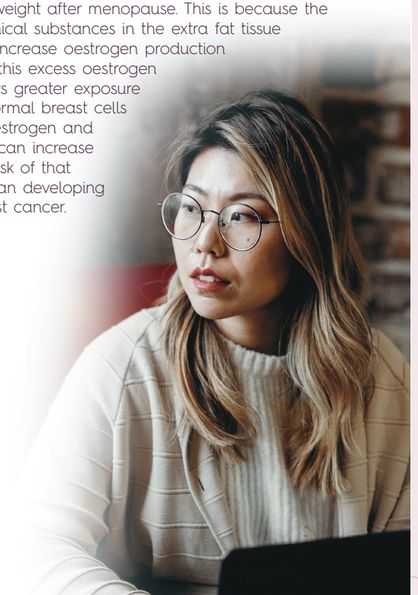


Figure 2. *After menopause, testosterone produced by the adrenal gland (situated above the kidneys) or from the testes in men is converted to oestrogen in tissue cells*

HOW DOES OESTROGEN PLAY A ROLE *in breast cancer?*

70-80% of breast cancers have "hormone receptor" on the surface of the breast cancer cell and thus oestrogen in the body can support the cancer cell's growth. These ER/PR positive breast cancers can thrive under the stimulating properties of oestrogen found in body fluids and the blood stream. As tissues in a woman's body have more oestrogen exposure throughout their lifetime, breast cancer is more common in women as they become older. But as men also have circulating oestrogen in their body, breast cancer can also develop in men. Breast cancer is also more commonly found in women who are overweight after menopause. This is because the chemical substances in the extra fat tissue can increase oestrogen production and this excess oestrogen allows greater exposure of normal breast cells to oestrogen and thus can increase the risk of that woman developing breast cancer.



HOW IS OESTROGEN TARGETED *in breast cancer?*

Since the source and level of oestrogen is different in women before and after menopause, treatment strategies differ in these situations.

Mode of Action	Treatment examples	Administration and other properties	Effects of menopausal state
In younger women who have ovaries that are still producing oestrogen. "Shutting off" ovaries leads to oestrogen production levels diminishing very significantly (thus this woman enters menopause)	· Goserelin "Zoladex" · Removal of both ovaries (bilateral oophorectomy)	· Injected into tummy fat every month. · Places women into menopause whilst monthly injections are given · Surgery to remove both ovaries · Irreversible process of inducing menopause · Usually considered in patients closer to natural menopause Or · In a breast cancer patient who is known to have the high risk BRCA gene and wants to reduce risk of ovarian cancer Or · In patients with metastatic/ advanced breast cancer to simplify "shutting off" the ovaries and thus not needing to have monthly injections of goserelin	· Used in women before natural menopause · Occasionally can be used in isolation to treat breast cancer · More commonly is combined with other drug treatments such as Tamoxifen or Letrozole. *(Note: Some young women who are still menstruating at the time they are diagnosed with breast cancer, will be recommended to have Goserelin during chemotherapy. This is to try and protect the ovaries from being permanently "shut off" by the chemotherapy.*
Blocking the oestrogen receptor protein	Tamoxifen (Selective estrogen receptor modulator – SERM)	Oral medication taken daily. · It blocks the oestrogen receptor so that the body's natural oestrogen cannot attach and exert its stimulating effects on the cancer cell. · A good by-product is that it can improve health in other tissues such as the bone and uterus.	· Can be used in women before or after menopause. · Can be used alone or in combination with treatment that induces menopause.
	Fulvestrant (Selective estrogen receptor degrader – SERD)	· Muscle injection in both buttocks every month (two injections in the first month). · It attaches onto the oestrogen receptor and destroys the receptor. · Newer, oral versions of this drug is currently being studied in clinical trials and when shown to be as or more effective than fulvestrant, will make it much easier for patients to receive.	
Blocking aromatase (the hormone in the body that switches testosterone into oestrogen)	Letrozole, Anastrozole, Exemestane (these are collectively called Aromatase Inhibitors-AI)	· Oral medication taken daily · Blocks the function of aromatase and reduces the conversion of testosterone to oestrogen	· Can only be used in women after natural or induced menopause.