**Normal Physiology** (females and males)
- Sexual development and fertility
- Reproductive cycles and pregnancy
- Liver, fat, and bone cell metabolism
- Cardiovascular and neuronal activity

**Disease and Medicine**
- Mitogenic role in breast and uterine cancers
  
  *(Aromatase Inhibitors, Antiestrogens)*
- Osteoporosis
  
  *(Post-menopausal HRT)*
- Steroidal contraceptives

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**Estrogen Receptors:**

*Ligand-Regulated, DNA-Binding Transcription Factors*

<table>
<thead>
<tr>
<th>AF-1</th>
<th>DNA</th>
<th>Ligand / AF-2</th>
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</thead>
<tbody>
<tr>
<td>hERα</td>
<td>1</td>
<td>180 263 302</td>
</tr>
<tr>
<td></td>
<td></td>
<td>552 595</td>
</tr>
<tr>
<td>28%</td>
<td>96%</td>
<td>58%</td>
</tr>
</tbody>
</table>

- **17β-Estradiol** (a natural estrogen)
- **Hydroxytamoxifen** (a SERM)
- **Raloxifene** (a SERM)

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**Estrogen Signaling Pathways**

- **Extracellular Space**
- **Cytoplasm**
- **Nucleus**

  - **Direct**
  - **Indirect or “Tethered”**
  - **Other Transcription Factors**

- Activation of protein kinases:
  - MAPKs, PI3K, PKC
- Production/release of cytoplasmic signals:
  - cAMP, Ca²⁺, PI(3,4,5)P₃
- e.g., orphan G protein-coupled receptor (GPR30)
- e.g., G-proteins, Src, Ras, GF receptors, MNAR

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*www.cancer.gov*
Understanding Cancer Series: Estrogen Receptors/SERMs