Breast Cancer

An Endocrinologist's Perspective

F.V. Nowak, M.D., Ph.D.
Ohio University
22 June, 2004

Hormonal Contribution to Breast Development

- Hormones involved in mammary development and function:
  - estrogen
  - progesterone
  - thyroid hormone
  - prolactin
  - growth hormone
  - cortisol
  - oxytocin

Breast Cancer

- Presentation is most common as a lump in the breast.
- Incidence currently in the U.S. is 1/8 women.
- Metastatic breast cancer is currently not considered a curable disease.

Risk Factors for Breast Cancer

www.bcra.nci.nih.gov/brc
Gail model

- Heredity/family history *
- Age at menarche *
- Diet
- Hormone usage
- Obesity
- Age at menopause
- Child bearing and fertility *
- Other tumors/benign breast disease *
- Irradiation
- Sedentary life style

Diet and Risk for Breast Cancer

- High intake of folate, calcium and vitamin D are protective.
- High alcohol intake increases risk.
  - decreased clearance of carcinogens
  - toxic effects of alcohol metabolites
- Obesity decreases risk before menopause and increases risk after menopause.

Patient Assessment

- Clinical staging
- The three most important prognostic factors
  - 1. Tumor size
  - 2. Axillary lymph nodes
  - 3. ER+ *vs*. ER- (PR)
- Growth factors and their receptors

Estrogen and Progesterone Receptors

- Are present in 90% of carcinomas of lobular origin
- Are present in 55% of adenocarcinomas or ductal carcinomas
- Are present less frequently in other types
- The presence of ER denotes an improved prognosis
- ER+ tumors have $\geq$ 10 fmol receptor protein/mg cytosol protein; ER++ tumors have $\geq$ 100 fmol receptor protein/mg

Estrogen and Progesterone Receptors

- ER++ tumors also have a better response to hormonal therapies than do ER+ tumors
- Progesterone receptors are also routinely measured as an indicator of ER functionality
- The presence or absence of ER and PR is used to design adjunctive therapies

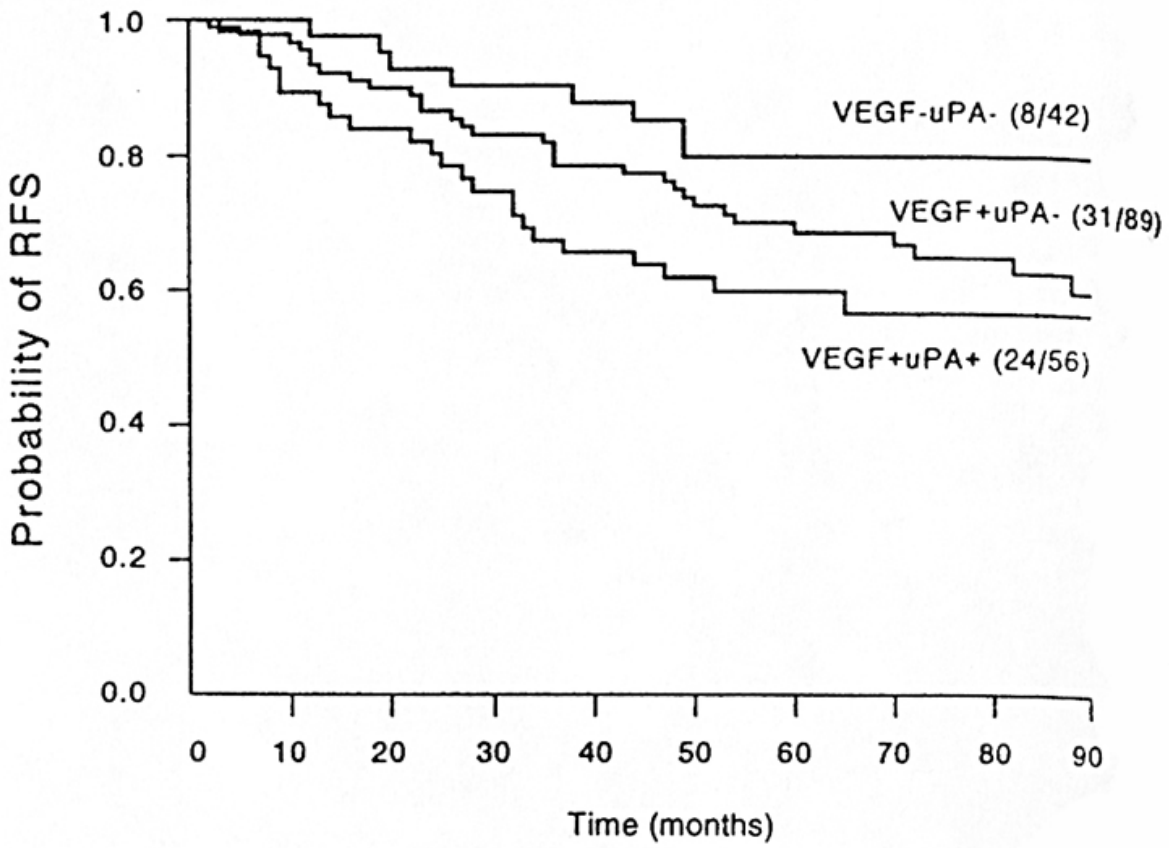
Percentages of tumors with different receptor status

Receptor Status	Premenopausal	Postmenopausal
ER+/ PR+	45	63
ER+/ PR-	12	15
ER-/ PR-	28	17
ER-/ PR+	15	5

Adapted from KI Bland et al. Menopausal status as a factor in the distribution of estrogen and progestin receptors in breast cancer. Surg Forum 32:410, 1981.

High VEGF and uPA Predict Decreased Survival

VEGF=vascular endothelial growth factor
uPA=urokinase-type plasminogen activator



U Eppenberger et al. J Clin Oncol 16:3129, 1998.

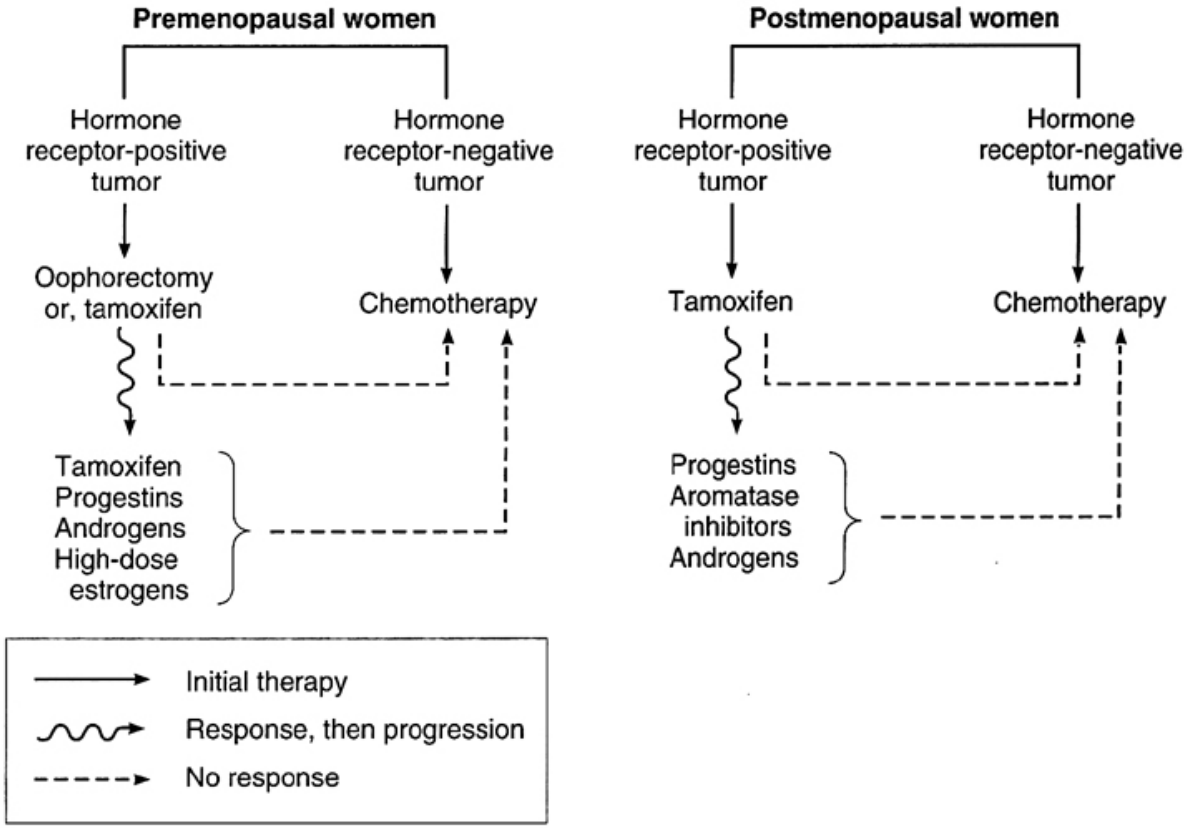
Breast Cancer--Therapy

- Surgery
- Chemotherapy
- Hormonal therapy/ endocrine ablation (surgical or chemical)

Breast Cancer

- Hormonal therapies are used for prevention in high risk patients
- as well as for prevention or treatment of recurrence
- Treatment modalities include oophorectomy or GnRH analogs, antiestrogens, adrenalectomy or aminoglutethimide, progestins, androgens and aromatase inhibitors.

Therapies for Breast Cancer



Treatment algorithm for advanced breast cancer in women.

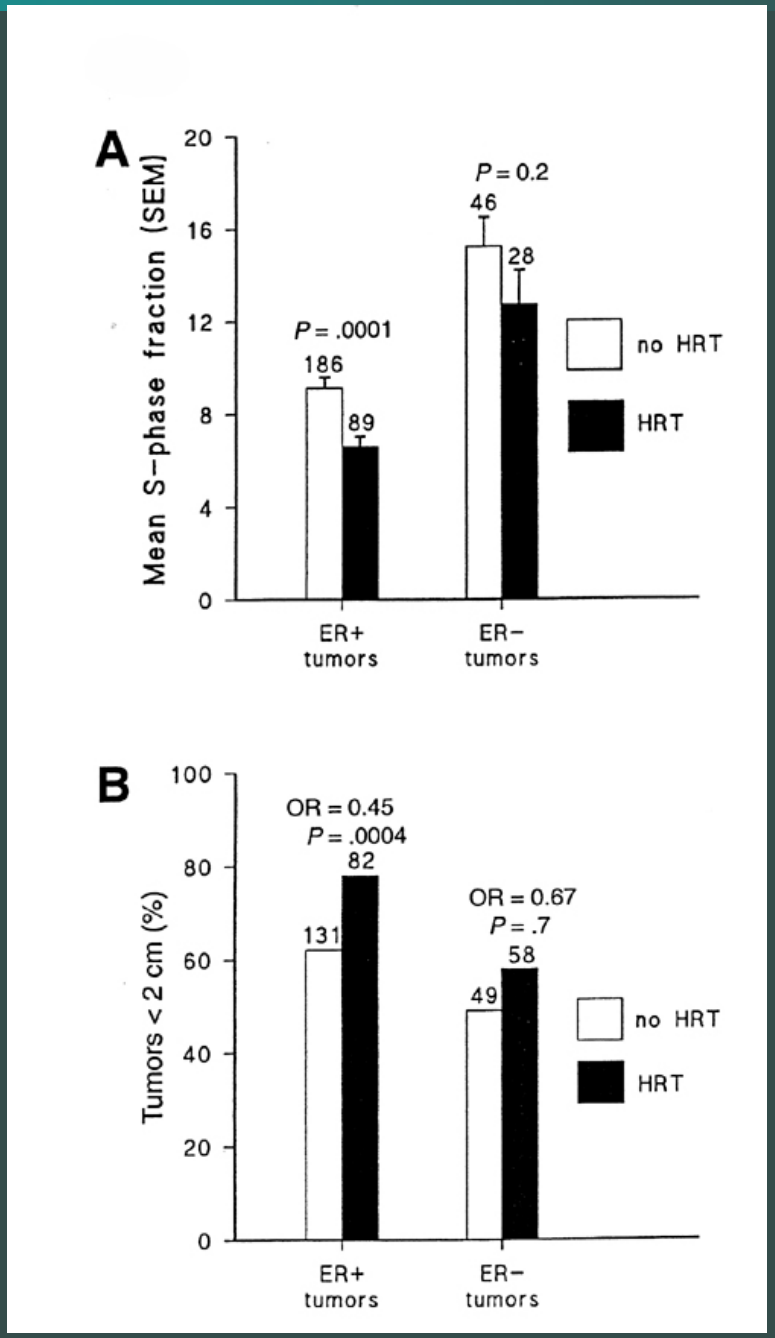
Breast Cancer in Women Treated with HRT

- Consensus is that there is an increased incidence of breast cancer in women treated with long term estrogen alone or combination HRT (not sequential).
- Women who use 5 years of HRT are at 0.2% absolute increased risk, 10 years, 0.6%, 15 years, 1.2%.
- Despite the increased incidence, an increase in mortality from breast cancer has not been consistently shown.
- This may be due in part to the observed differences in this population, i.e., smaller tumor size, greater degree of histological differentiation and lower proliferation rates, measured as S-phase fraction.

Breast Cancer in Women Treated with HRT

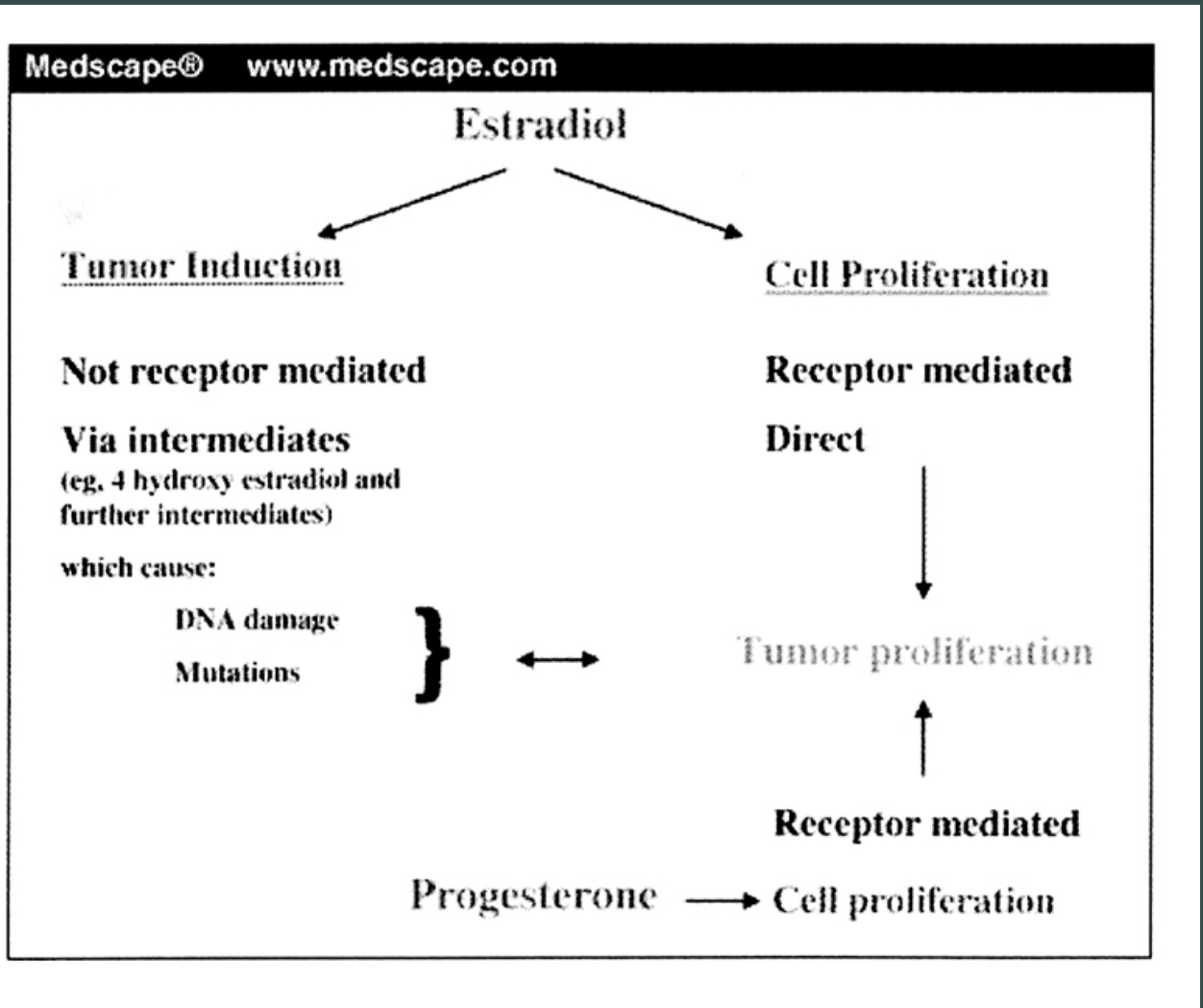
- The Million Women Study showed no effect of dose, origin or route of delivery of estrogen on risk.
- However this study has been called into question and conflicts with other observations
  - plasma levels and duration of exposure to estrogen are accepted factors in determination of patient risk.
  - Dose and route of delivery affect plasma estrogen levels.
  - A large meta analysis has shown RR of recurrence in breast cancer survivors using HRT (E2 only) to be 0.72 compared with non-users.

Effect of HRT on Tumor Size and Proliferation



K Holli et al. J Clin Oncol 16:3115, 1998.

Possible Mechanism of Tumor Induction by HRT

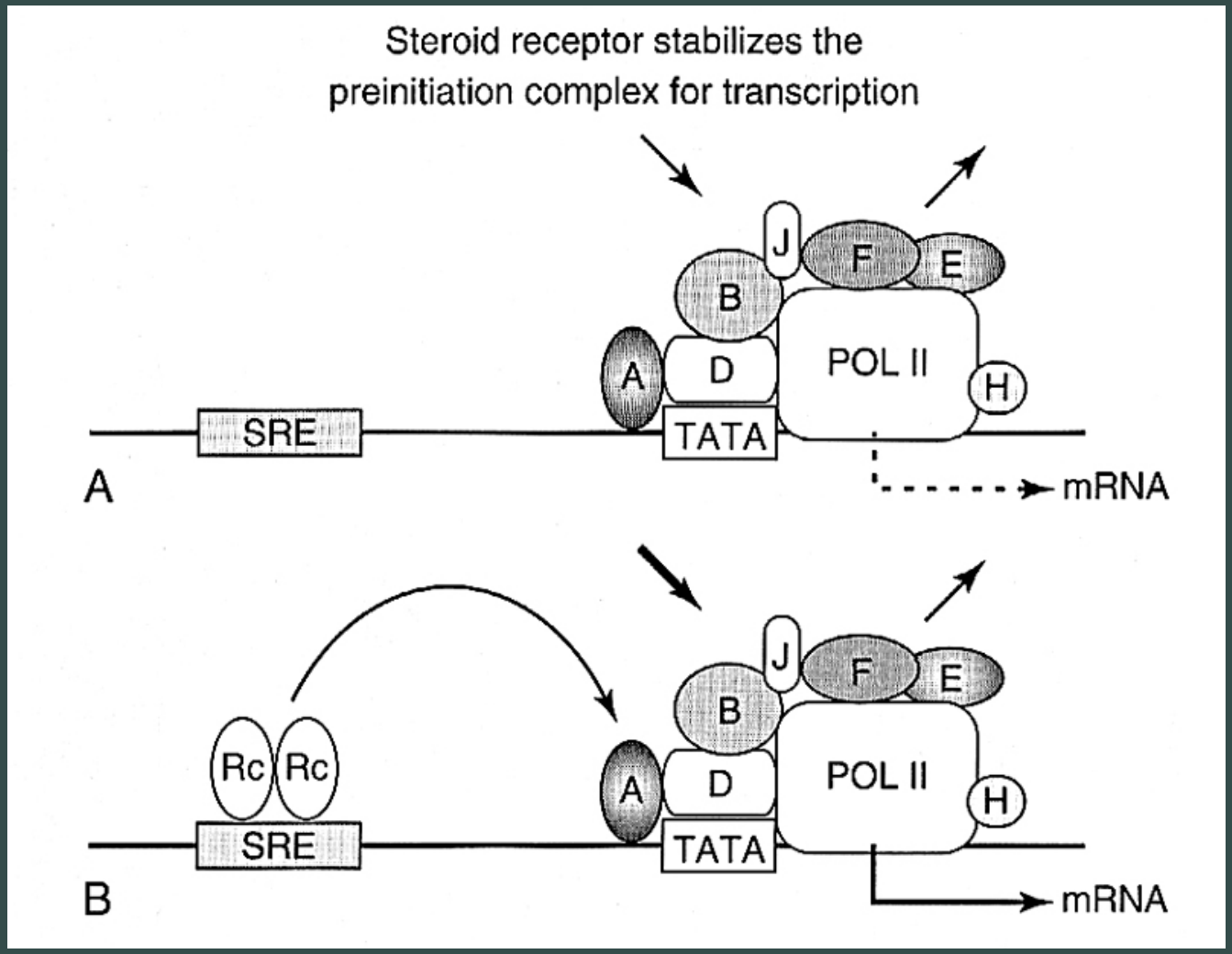


HS Jacobs, Medscape Women's Health 5 (4), 2000.

Estrogen Analogs

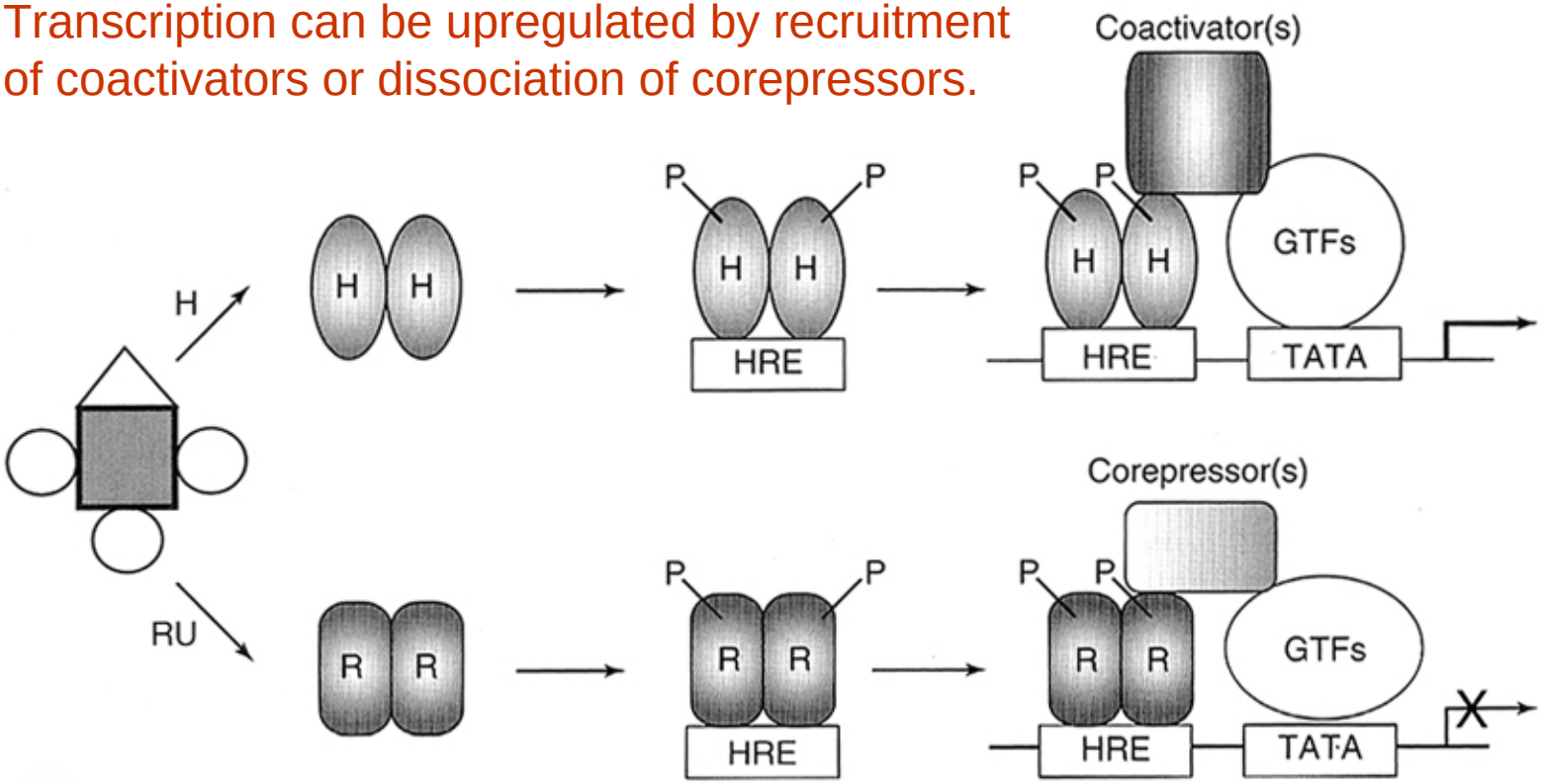
- Review of basic mechanism of steroid action
- Biochemical basis for agonist and antagonist actions
- SERMs (Selective Estrogen Receptor Modulators) action is tissue specific
  - e.g., tamoxifen, raloxifene

Basic Mechanism of Steroid Hormone Action



Biochemical Basis for Selective Receptor Interactions

Transcription can be upregulated by recruitment of coactivators or dissociation of corepressors.



Transcription can be downregulated by recruitment of corepressors.

Factors Modulating Ligand Receptor Activity and Biological Effect in Different Tissues

- Receptor type and concentration
- Ligand type and concentration
- Concentrations and types of coactivators and corepressors; recruitment by ligand receptor complex of coactivators or corepressors
- Phosphorylation state of receptor
- Cross talk with other pathways

ER alpha and ER beta

- Two structurally distinct estrogen receptors
- Both are expressed in normal breast ($\beta > \alpha$) and breast tumors ($\alpha > \beta$)
- Different tissue distribution
- Interactions with coactivators and corepressors differ
- One may stimulate expression of a given gene while the other inhibits it

Tamoxifen

- There is now over 30 years' experience with the use of tamoxifen for breast cancer.
- It can be used as a chemoprotective agent in high risk patients, as adjunctive therapy to prevent recurrence and to induce remission in recurrent disease
- In an overview of 37,000 women in randomised trials for the use of T in early breast cancer, it was concluded that T reduces recurrence and improves breast cancer survival. The effect is greater with longer duration of therapy, up to an average of 5 years.
- There was a decrease in cancers of the contralateral breast, an increase in incidence of endometrial cancers and no effect on colorectal cancers.

- However, overall survival was not improved mainly due to an increase in thromboembolic events.
- Tamoxifen should not be given concurrently with chemotherapy.
- The current standard is five years of tamoxifen therapy. Trials are underway to look at longer durations of therapy.
- Additional trials are needed to investigate other options such as lowering the dose from 20 mg/day, using alternate day therapy, and combining tamoxifen with HRT.

Predictors of Tamoxifen Effectiveness

- ERα
  - 10% response in ER-
  - 50% response in ER+
  - 60% response in ER++
- PR—presence indicates functional E_2 pathway
- Bcl-2 (involved in control of cell death as an antiapoptotic molecule).
  - 62% response in Bcl-2+,
  - 49% response in Bcl-2-
  - independent of ER or nodal status

Raloxifene

- Postmenopausal women who are at average risk for breast cancer who take raloxifene for 3 years for prevention of osteoporosis will realize a 70% reduction in their breast cancer risk, without any increase in risk for endometrial cancer.
- The STAR trail is an ongoing direct comparison of tamoxifen with raloxifene for the primary prevention of breast cancer.

Endocrine-Resistant Breast Cancer

- One third of ER positive recurrent breast cancers fail to respond to endocrine therapy.
- Most endocrine responsive breast tumors ultimately become endocrine resistant.
- Tamoxifen resistance may be due to modified metabolism or stimulation of ovarian estrogen production.
- Several growth factors and their intracellular signalling pathways can stimulate ER activity in the absence of a ligand.

Endocrine-Resistant Breast Cancer

- Qualitative or quantitative changes in ER-related coactivators and corepressors could contribute to development of resistance.
- ER beta may play a role.
- Loss of ER alpha expression may cause resistance to endocrine therapies
  - endocrine based therapies could select for ER negative cells
  - hypoxic microenvironments may result in loss of ER expression

Aromatase Inhibitors

- Anastrozole and letrozole are third generation non-steroidal drugs that almost completely block the activity of peripheral aromatase and in post-menopausal patients effect a substantial decrease in circulating levels of estrogens.
- In comparison with tamoxifen or tamoxifen plus anastrazole, anastrazole showed a 17% reduction in events. Letrozole also may result in a significantly higher time to progression than tamoxifen in patients with MBC.
- Exemestane is a steroidal, selective aromatase inhibitor.

HER2

- High levels of the human growth factor receptor HER2 may be tumorigenic.
- HER1 or HER2 is over-expressed in 30% of primary human breast cancers. These patients show a worse prognosis with overall 50% survival after 90 months compared to 70% with HER2 negative tumors. This may be due to ligand-independent transactivation of ER target genes or other intracellular signalling pathways.
- Anti-HER2 antibodies (trastuzumab) combined with chemotherapy, show a small but significant improvement in response compared with chemotherapy alone.

New Options for Therapy

- Fulvestrant, a pure antiestrogen
  - Acts by inhibiting dimerization of receptor-ligand complex.
  - Was effective against tamoxifen resistant tumors in preclinical trials.
  - Trials of combined therapy with fulvestrant plus anastrazole and of fulvestrant in patients who had progressed on prior treatment with anastrazole are in progress.

New Options for Therapy

- Intracellular hormone response machinery
  - EGF-R-specific tyrosine kinase inhibitors may be effective in breast cancers over-expressing HER1 or HER2.
  - COX-2 inhibitors. COX-2 has been correlated with carcinogenesis, and may act by promoting angiogenesis and inducing aromatase.
  - Combinations of different signal transduction inhibitors may prove a more effective strategy.

New Options for Therapy

- New SERMs, estrogen and progestin antagonists, GnRH analogs, and aromatase inhibitors.
- Fenretinide, a vitamin A analog, decreased local recurrence in premenopausal women. It is being tested in healthy women receiving HRT.
- Other antiangiogenic agents
- Protease inhibitors

Primum non nocere.