Hormones and cancer

BSc Oncology Surgery

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Clinical Oncology Consultant Breast/ Lower GI

Oncology Associations-bad

- Death
- Suffering
- Hopelessness

- To do radiotherapy you have to be good at physics
- You have to work very hard and be very clever
- Very competitive

Oncology Associations- good

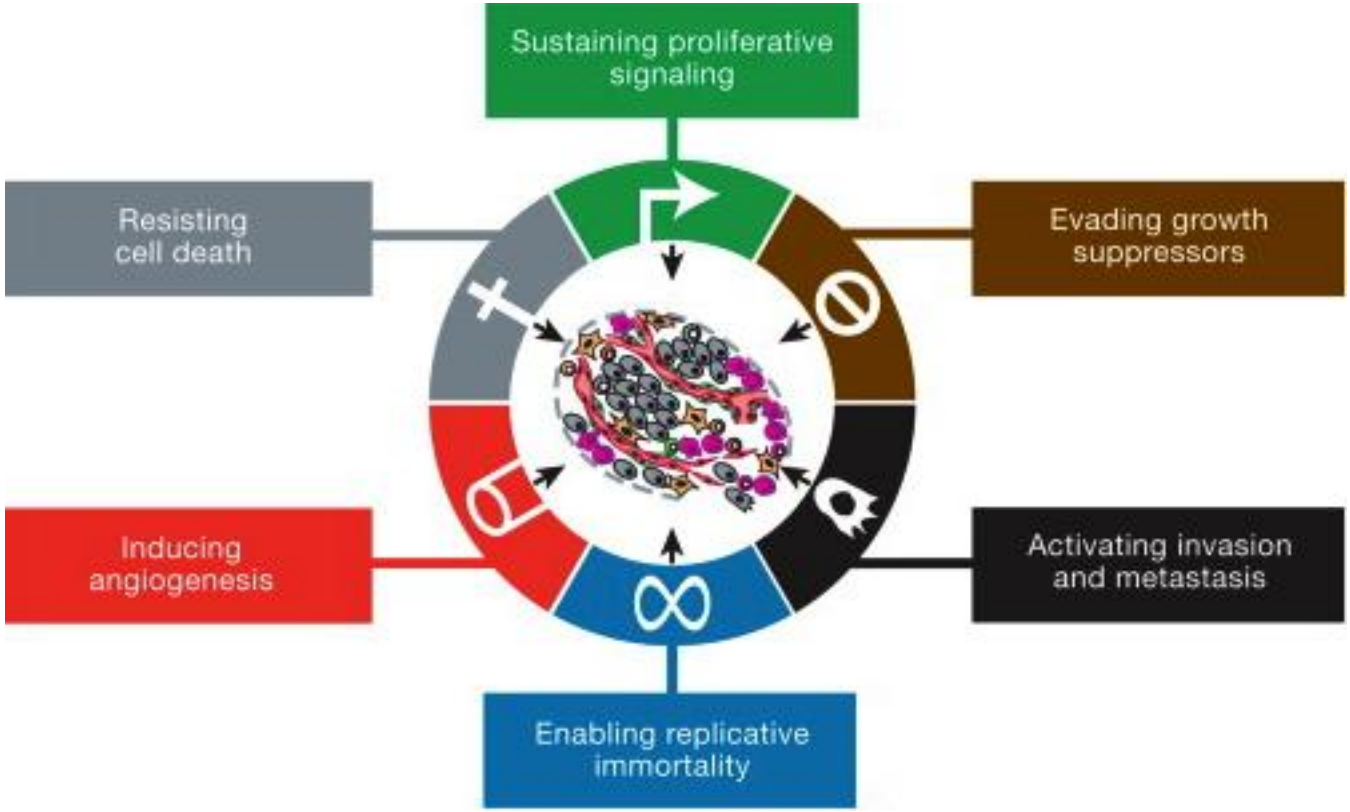
- New treatments all the time
- Good links with basic science
- Most treatments have good evidence base
- Committed staff
- Lots of patient contact/ rewarding

- Good on-call
- Good for private practice (depending…..)

Learning Objectives

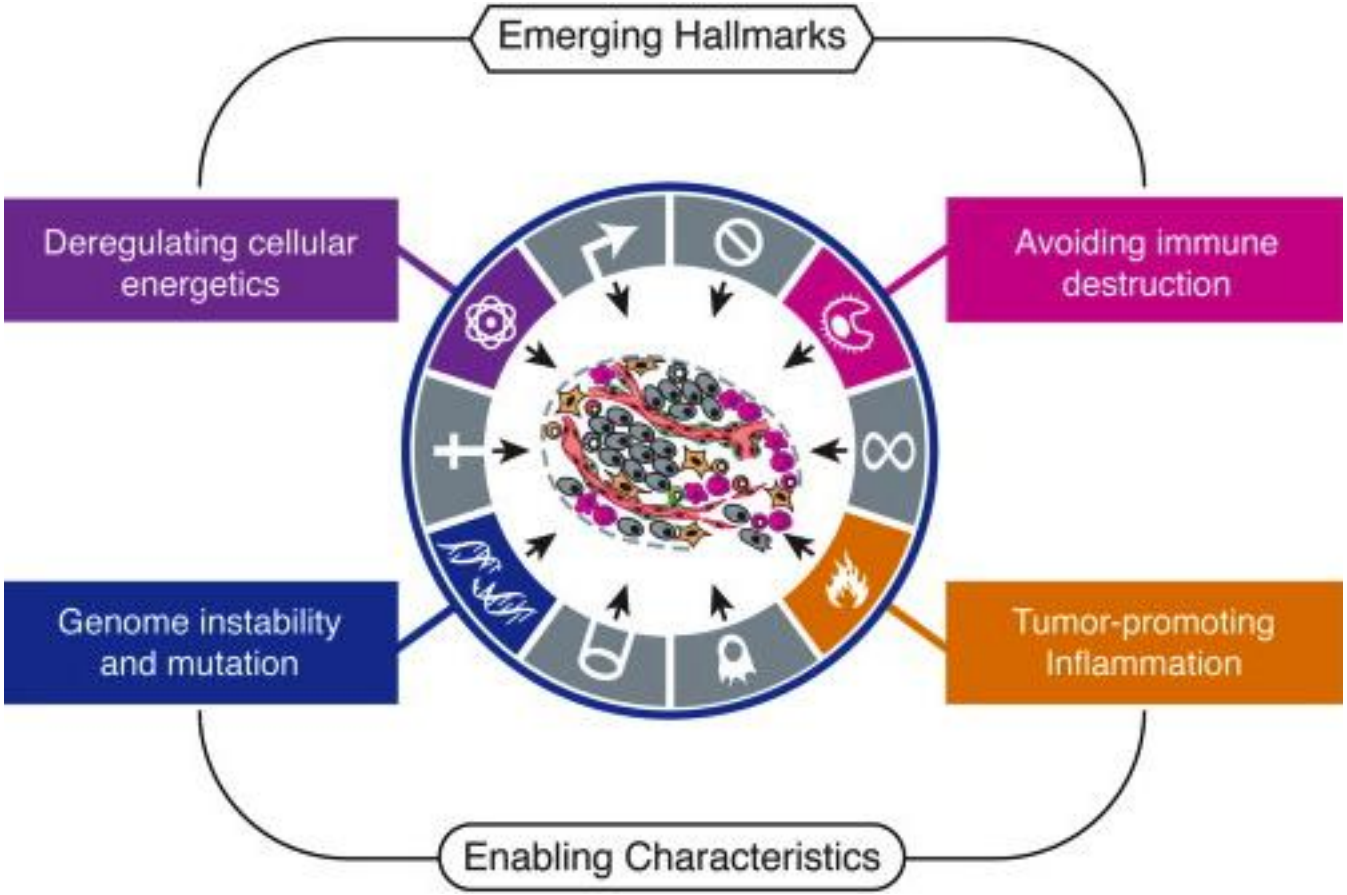
- Drivers of cancers
- Which cancers are driven by hormones
- Which cancers produce hormones
- How are they driven by hormones
- How can this be harnessed therapeutically
- Side effects of hormonal manipulation to control cancers
- New Drug Development
  - overcoming hormone resistance

Targets: The (Original) Hallmarks of Cancer



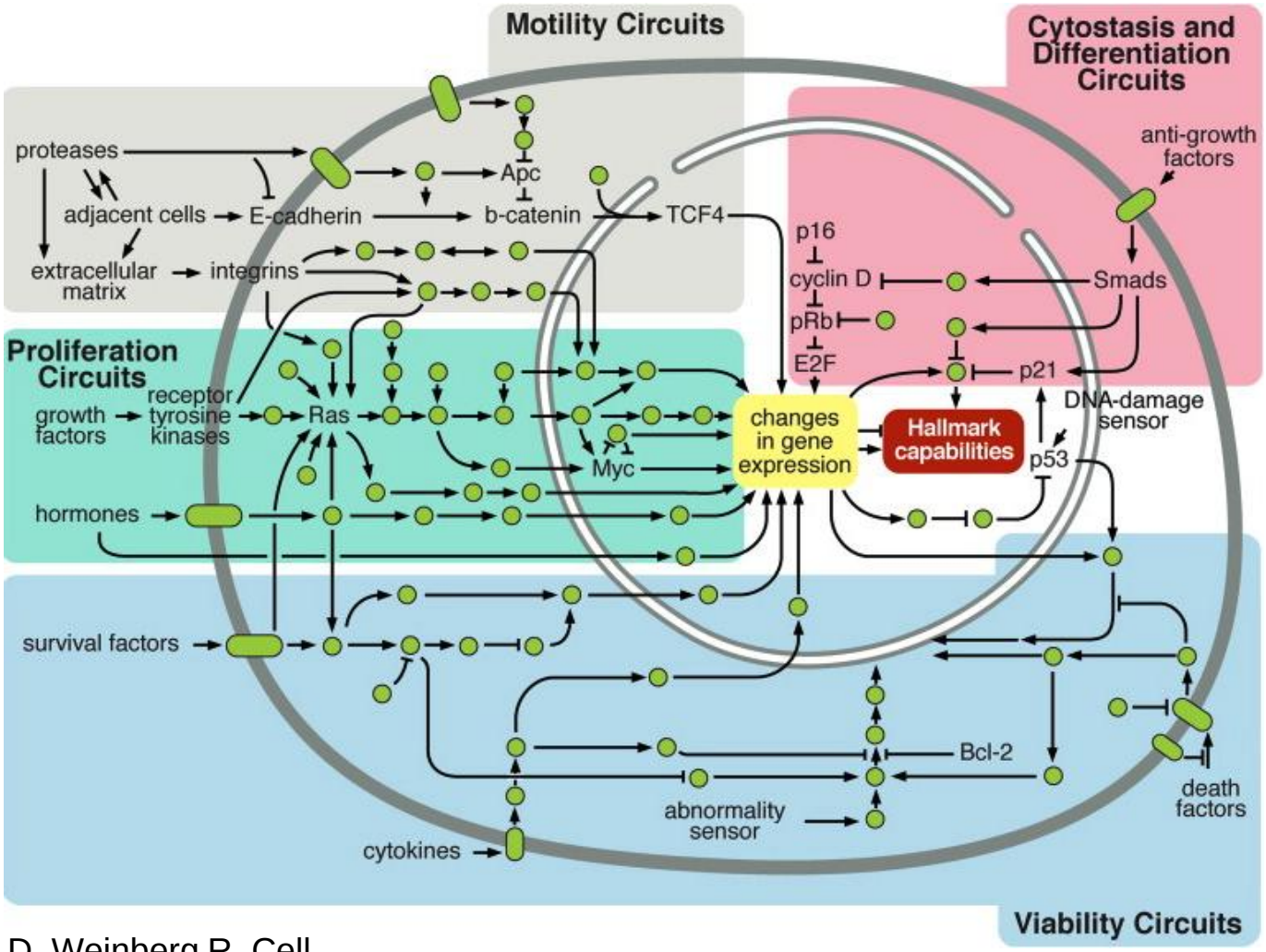
Hanahan, D., and Weinberg, R.A. (2000). The hallmarks of cancer. Cell 100, 57–70.

Updated Hallmarks of cancer



Hanahan D, Weinberg R. Cell, March 2011

The Complexity of cancers

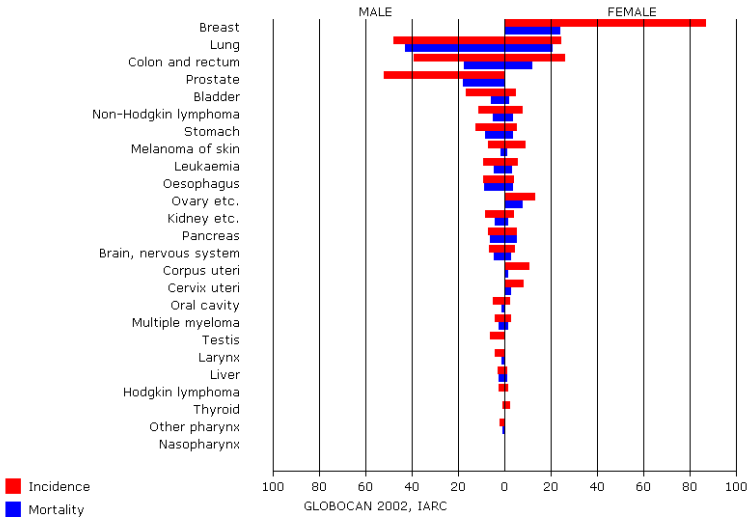


Hanahan D, Weinberg R. Cell,
Volume 144, 4 March 2011

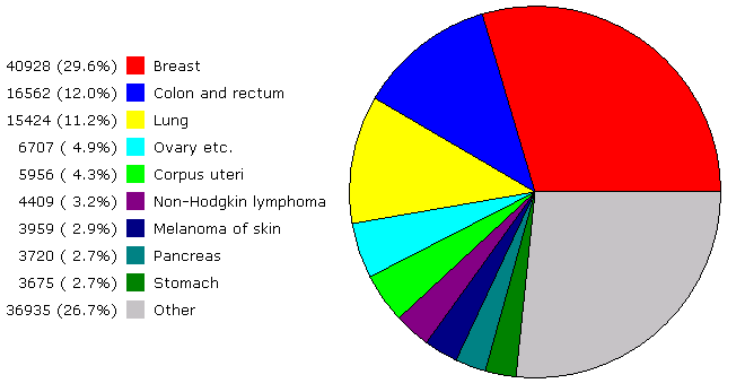
Treatment Modalities-Biological

- Monoclonal Antibodies
- Tyrosine Kinase Inhibitors
- Vaccines
- Gene Therapies
- Interleukin, interferon
- Endocrine therapy

United Kingdom
Age-Standardized rate per 100,000 (all ages)

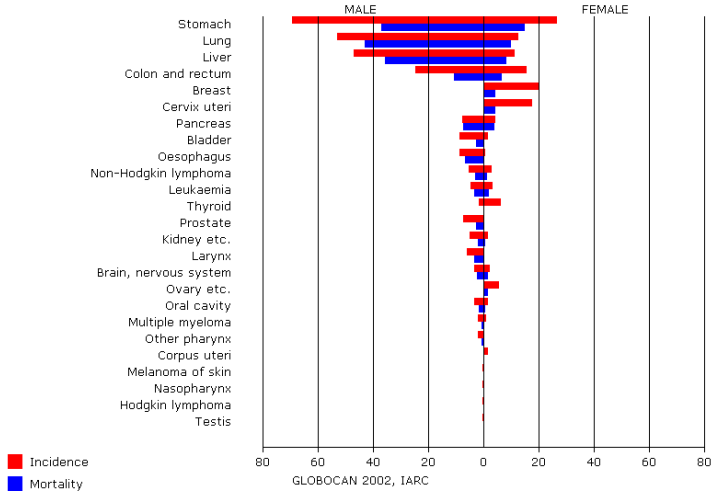


United Kingdom
New cancer cases (all ages), Females
Total: 138275

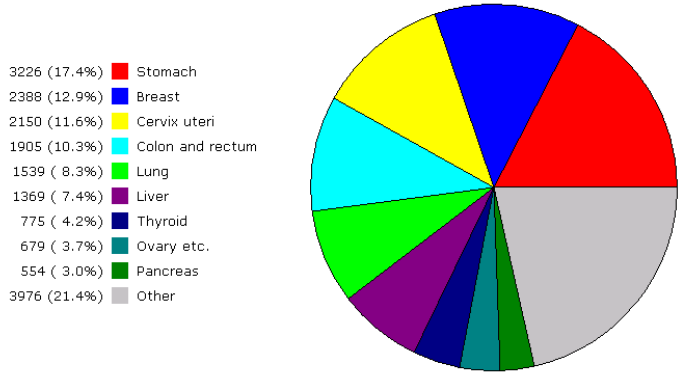


GLOBOCAN 2002, IARC

Korea, Republic of
Age-Standardized rate per 100,000 (all ages)



Korea, Democratic Republic of
New cancer cases (all ages), Females
Total: 18561



GLOBOCAN 2002, IARC

Commonest cancers in UK

- Lung
- Breast
- Prostate
- Colorectal

Most prevalent, relatively good prognosis

What is a hormone

- ‘Hormones are naturally occurring substances that are produced in specific parts of our bodies and act as chemical messengers. They travel through the blood to control the functions of other tissues and organs.’

Which cancers are hormonally driven (hormone dependent)

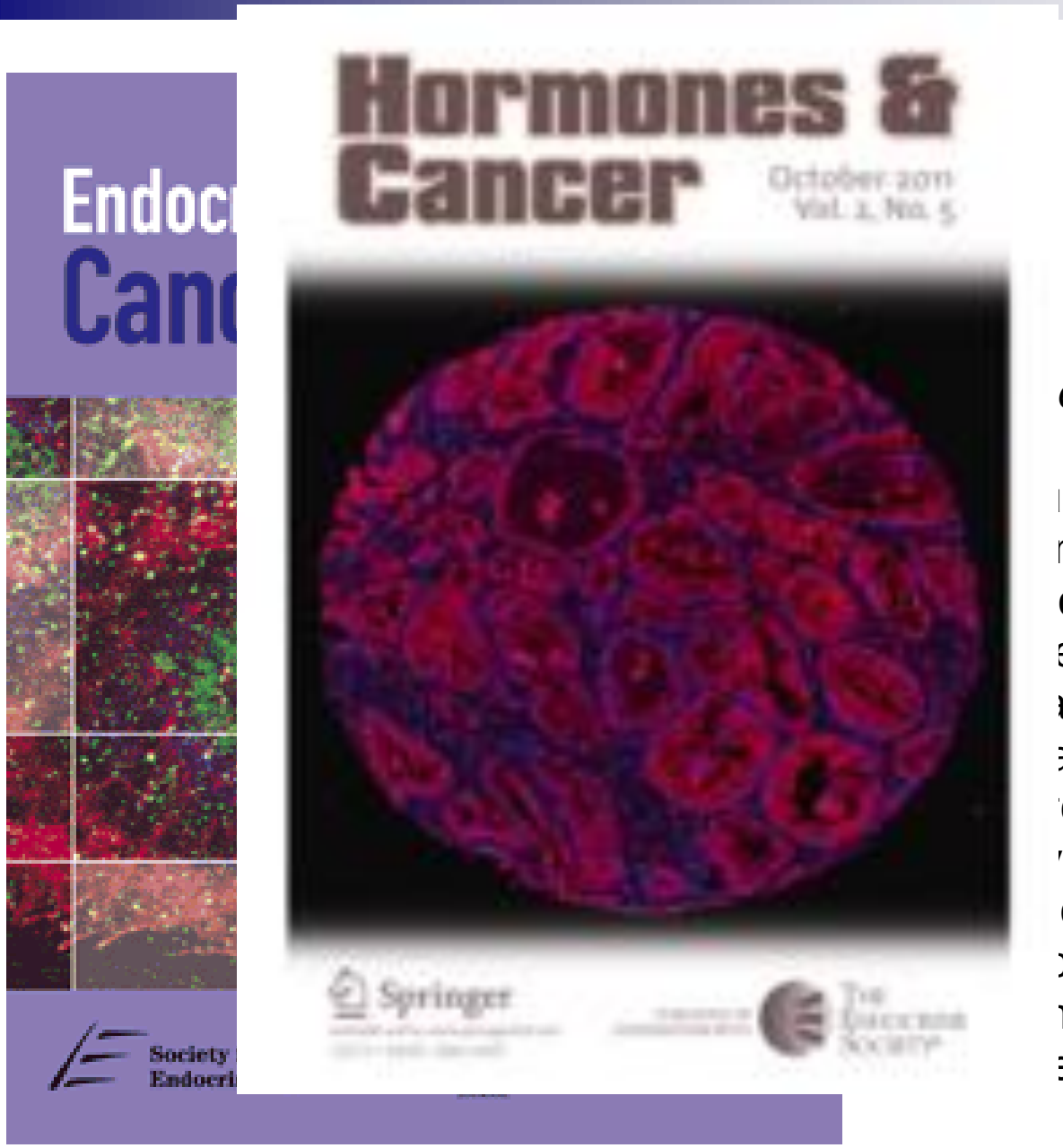
- **Breast**
- **Prostate**
- Endometrial
- Ovarian
- Vaginal clear cell carcinoma
  - Diethylstilbestrol is (DES) in pregnancy
- Hepatocellular carcinoma
  - Anabolic steroids
- Hepatic adenoma
  - Steroidal contraceptives

Hormones that cause cancers

- **Oestrogen**
  - breast cancer
  - womb cancer
- **Testosterone**
  - ?prostate cancer
- **Insulin**
  - Association with bowel, womb, pancreas and kidneys
- **Insulin-like growth factors** or IGFs (levels affected by insulin)
  - prostate
  - breast
  - bowel

What affects levels of hormones?

- Pregnancy/ menstrual/ breast-feeding history
- Exogenous hormones
  - HRT
  - OCP
  - anabolic steroids
- Life-style
  - weight
  - exercise
  - alcohol



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Cancers which produce hormones

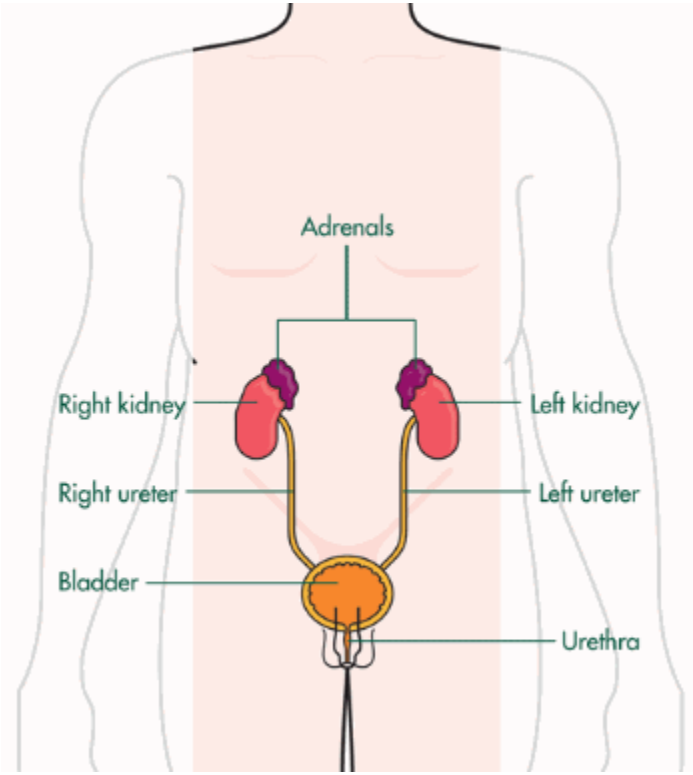
- Pituitary
- Adrenal
  - Cortex
  - medulla
- Parathyroid
- Ovarian
- Gastroenteropancreatic
- Thyroid (medullary)
- MEN1
- MEN2
- All cancers (notably, lung!)
  - Para-neoplastic syndrome
  - typically parathormone-like

Secretory pituitary cancers

- **Prolactin-secreting tumours**
  - most common type
  - F: infertility, amenorrhoea, gallactorrhoea
  - M: impotence, infertility
- **Growth hormone-secreting tumours**
  - acromegaly
- **TSH-secreting tumours**
  - extremely rare.
- **ACTH-secreting tumours**
  - Cushing's syndrome

Secretory adrenal cancers

- **Cortex:**
- **Glucocorticoid**
  - **Cushing's syndrome**.
- **Mineralocorticoids**
  - Conn’s syndrome
- **Sex hormones**



- **Medulla:**
- phaechromocytoma

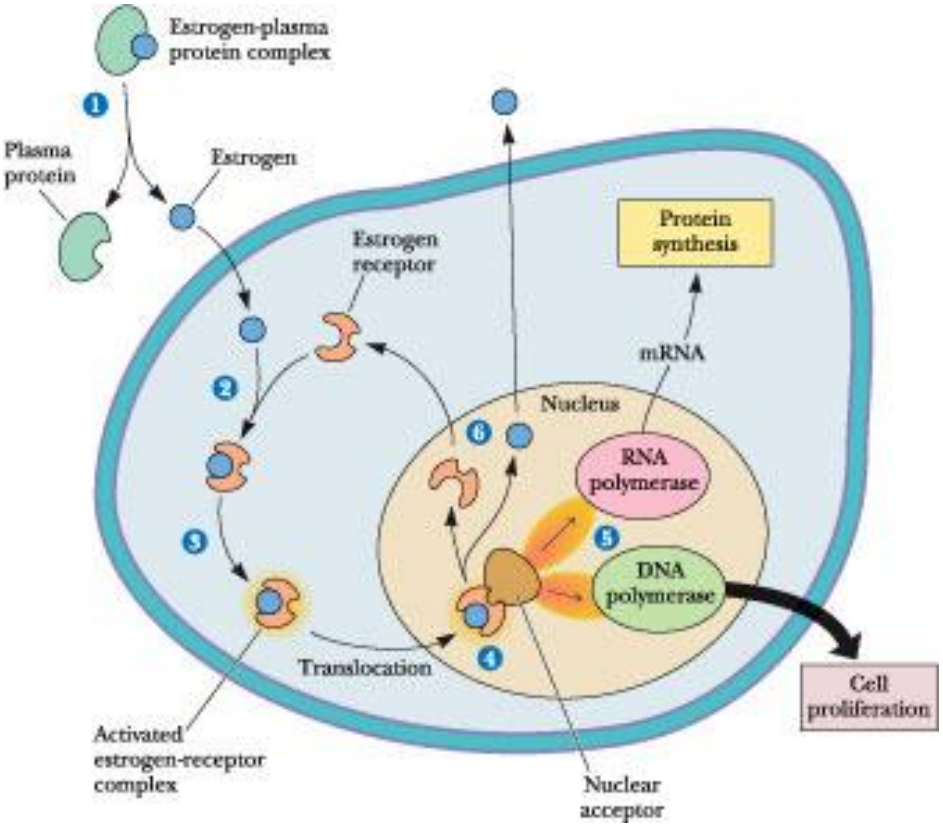
GEP tumours- gastroenteropancreatic tumours

- **Insulinomas**
- **Gastrinomas**
- **Somatostatinomas**
- **Glucagonomas**
- **VIPomas**

MEN 1 and 2

- MEN1: parathyroid, pancreas, bowel, pituitary, adrenal, carcinoid
- MEN2: medullary cell carcinoma thyroid, phaechromocytoma
- MEN2a: hyperplasia parathyroid
- MEN2b: multiple neuromas

How hormones drive cancers- transcriptional control



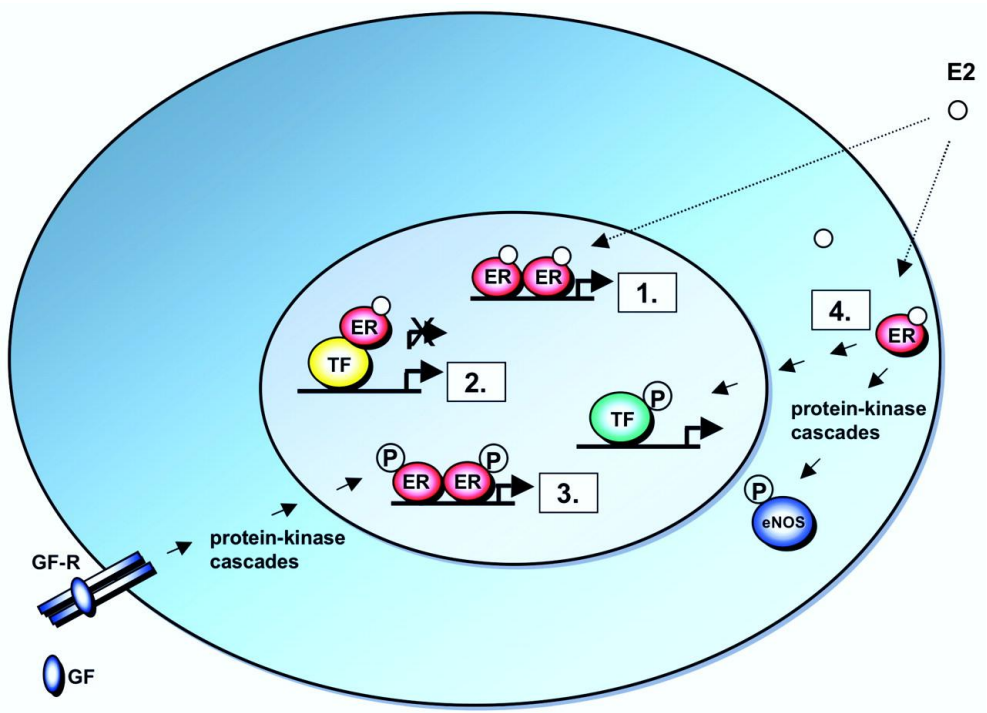
- A **transcription complex** initiates elongation of RNA synthesis at the **promoter**
- Sequence-specific **transcription factors** need to bind to initiate formation of the transcription complex
- Level of transcription is regulated by the activity of **transcription factors (e.g. ER)**

Sex hormone receptor ligand binding

- conformational changes
- disassociation from heat shock protein, phosphorylation, and dimerization.
- recruitment by dimers of coregulatory molecules
- binding to promotor region of target genes leading to gene transcription

- expression of these coregulators significant determinant of a tissue's response to steroidal stimulation

ER signalling

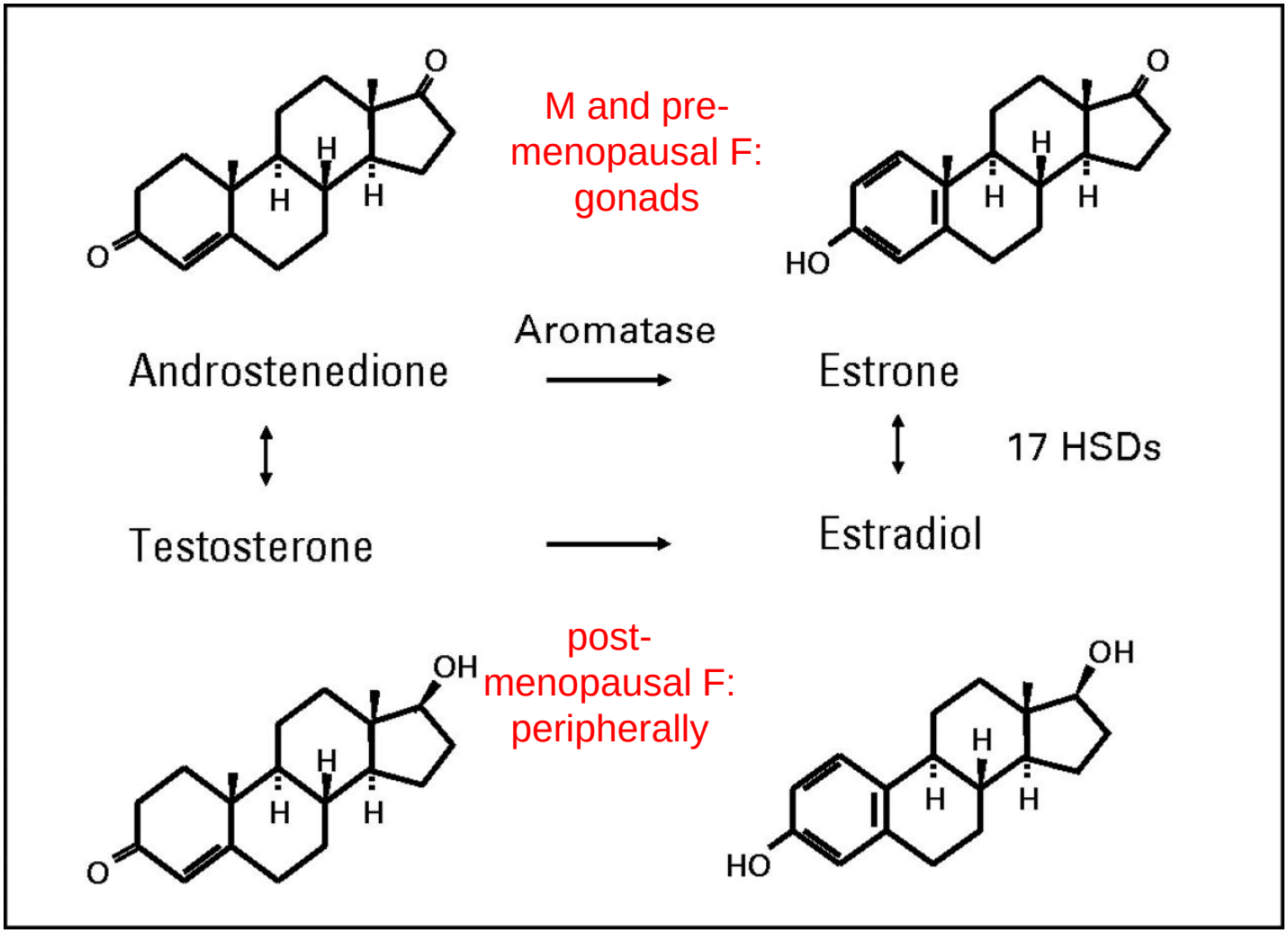


Björnström L , Sjöberg M Molecular Endocrinology 2005;19:833-842

1. **Classical:** nuclear E2-ERs bind directly to EREs in target gene promoters and recruit co-regulatory proteins.
2. **ERE-independent genomic actions**: nuclear E2-ER complexes are tethered through protein-protein interactions to a transcription factor complex (TF) that contacts the target gene promoter (e.g. Other modulators of cell signalling).
3. **Ligand-independent genomic actions**. GFs activate protein-kinase cascades, leading to phosphorylation (P) and activation of nuclear ERs at EREs.
4. **Nongenomic actions.** Membrane E2-ER complexes activate protein-kinase cascades, leading to altered functions of proteins in the cytoplasm, *e.g.* activation of eNOS*, or to regulation of gene expression through phosphorylation (P) and activation of a TF.

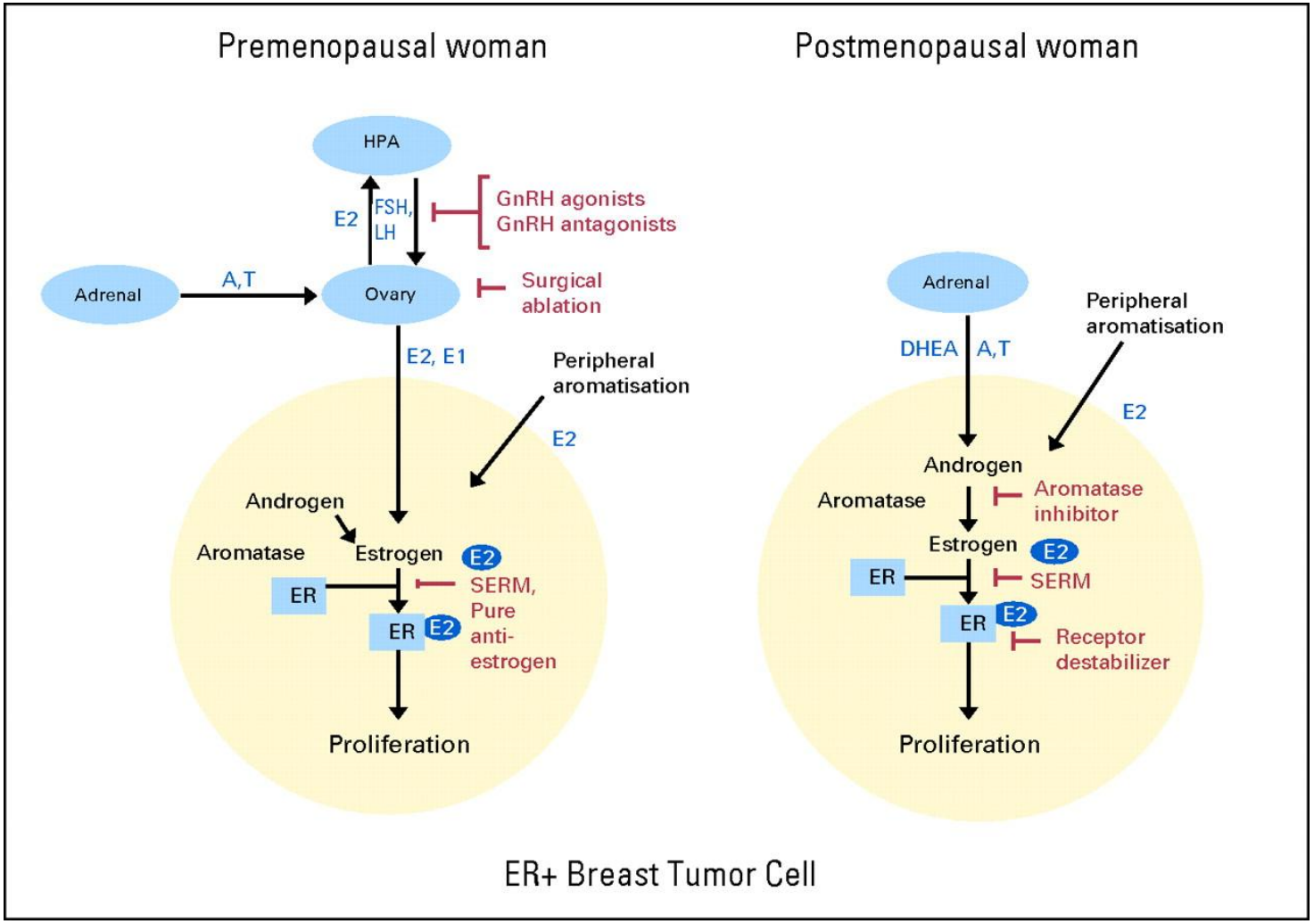
*nitric oxid synthetase

Major androgens and estrogens and their conversion by aromatase and 17 β-hydroxysteroid dehydrogenases (HSDs).



Folkerd E J , Dowsett M JCO 2010;28:4038-4044

The source of estrogens in breast tumour cells in pre- and postmenopausal women and the site of action of hormone intervention strategies.



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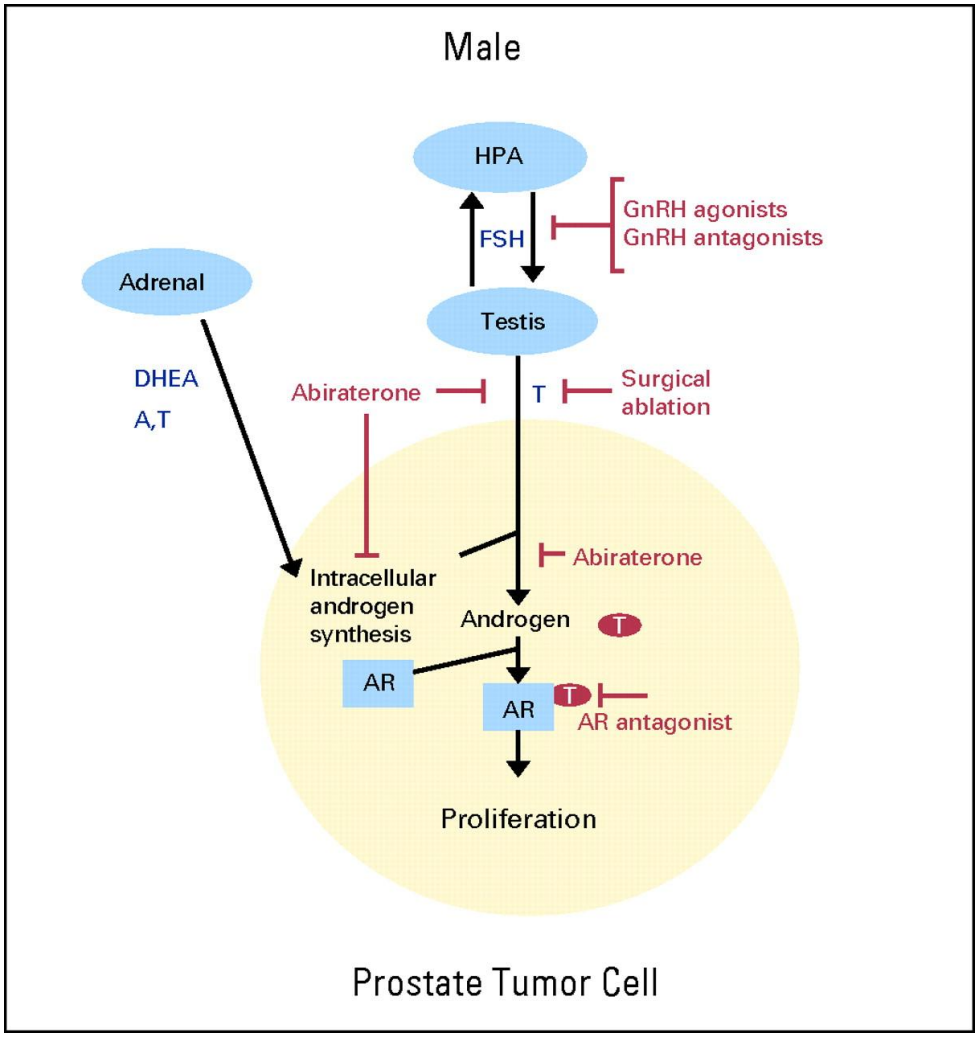
HPA, hypothalamic-pituitary-adrenal axis; FSH, follicle-stimulating hormone; E2, estradiol; GnRH, gonadotrophin-releasing hormone; LH, luteinizing hormone; A, androstenedione; T, testosterone; E1, estrone; DHEA, dihydroepiandrosterone; SERM, selective estrogen receptor modifier; ER, estrogen receptor

The source of androgens in prostate tumor cells and the site of action of hormone intervention strategies.



Folkerd E J , Dowsett M JCO 2010;28:4038-4044

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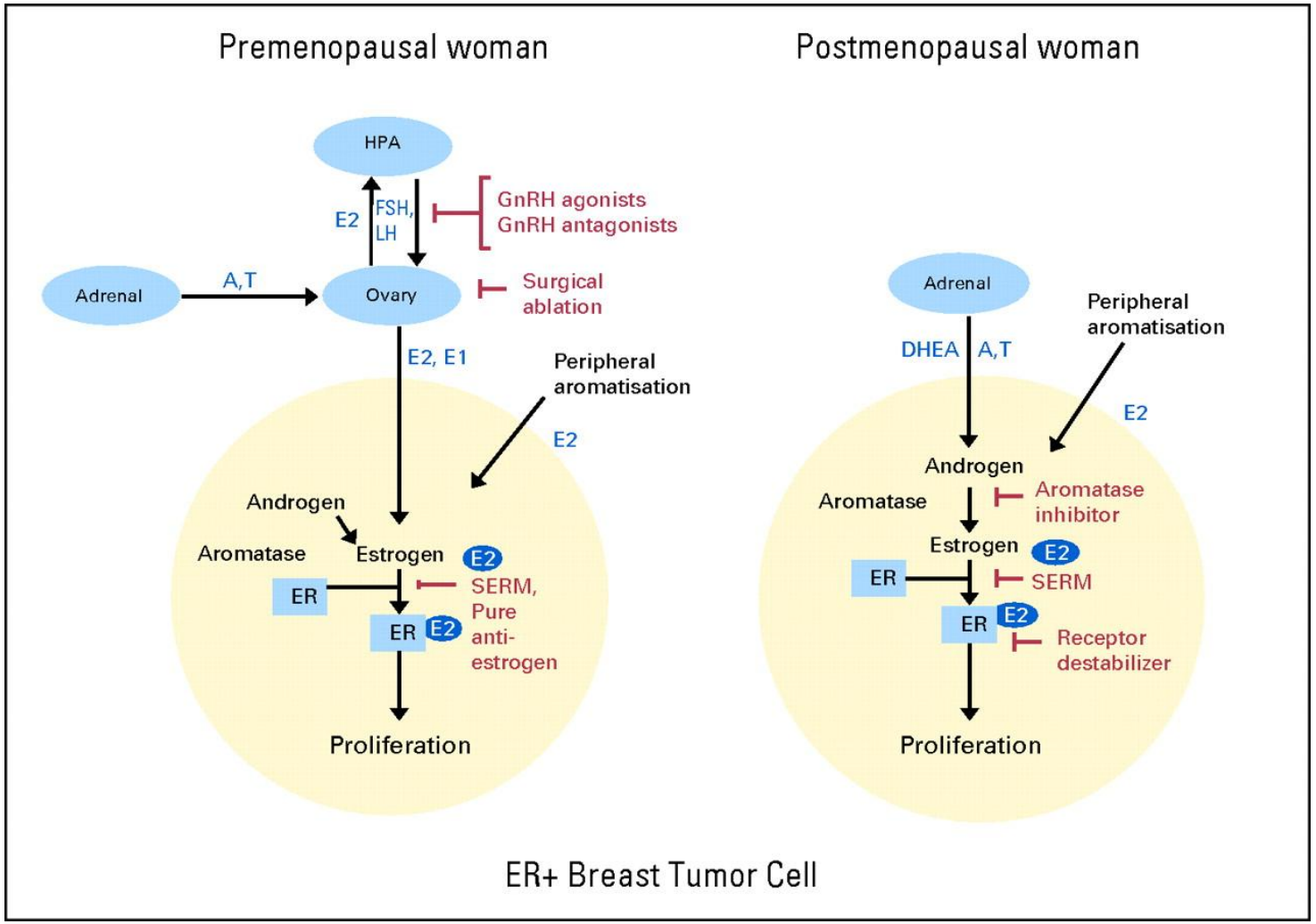
What goes wrong in cancer?

- effects of ligand-mediated receptor activation are normally highly regulated at many levels
  - transcriptional
  - post-transcriptional
  - post-translational levels
  - microRNAs
- In cancer cells
  - Normal regulatory mechanisms disturbed leading to uncontrolled proliferation

E2 as a risk for breast cancer

- HRT and OCP increase risk
- plasma levels of estradiol in postmenopausal women significantly correlate with breast cancer risk
- Early menarche and late menopause increase risk
- Breast feeding is protective
- Obesity increases risk
- Alcohol inceases risk

Anti-E2 treatment in ER pos cancer



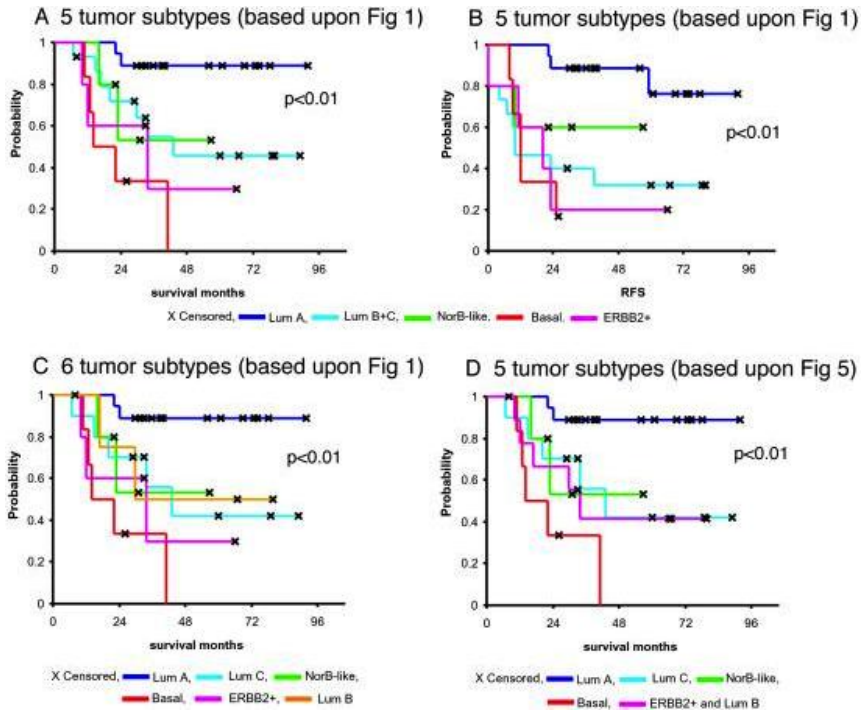
Blocking Oestrogen-signalling

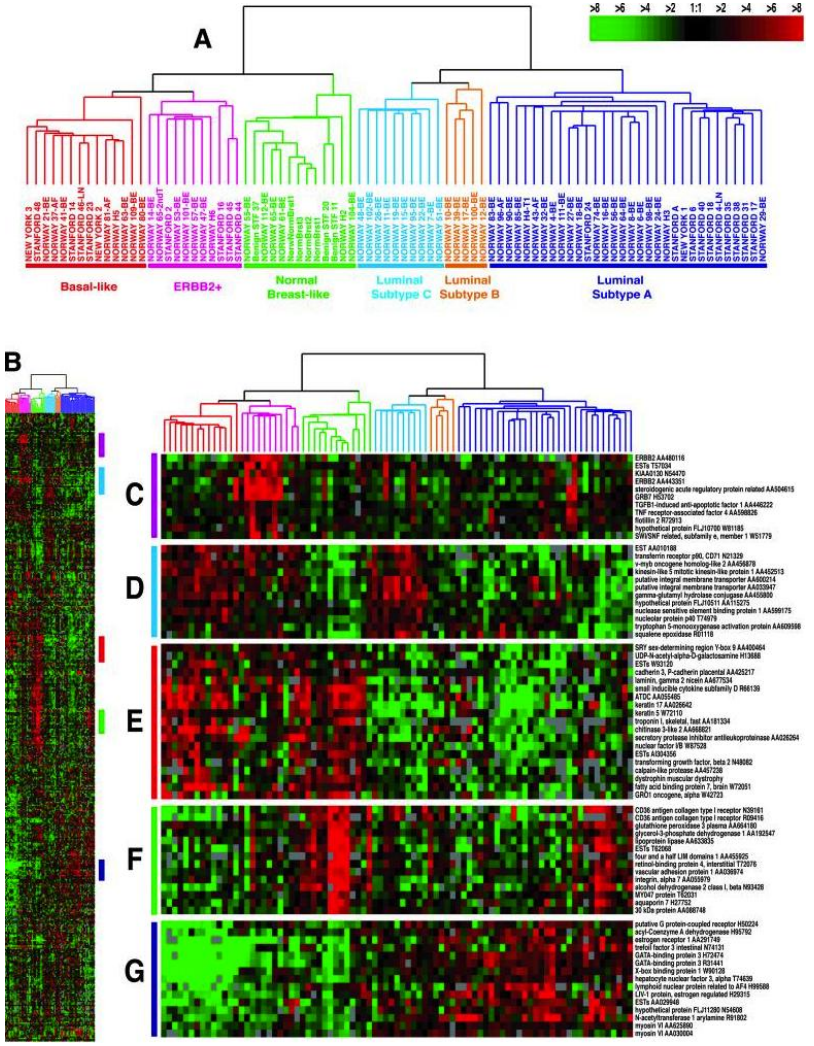
- Lowering E2 level
  - Premenopausal
    - ovarian ablation
    - luteinizing hormone-releasing hormone agonists
    - luteinizing hormone-releasing hormone antagonists
  - Postmenopausal women
    - aromatase inhibitors (AIs)
- Selective estrogen receptor modifiers
  - e.g tamoxifen-bind competitively to ER with tissue-specific effects
- Pure antiestrogen
  - fulvestrant, which binds competitively ER and leads to its degradation

Treatment Intent- definitions

- Radical
- Adjuvant
- Neoadjuvant
- Palliative

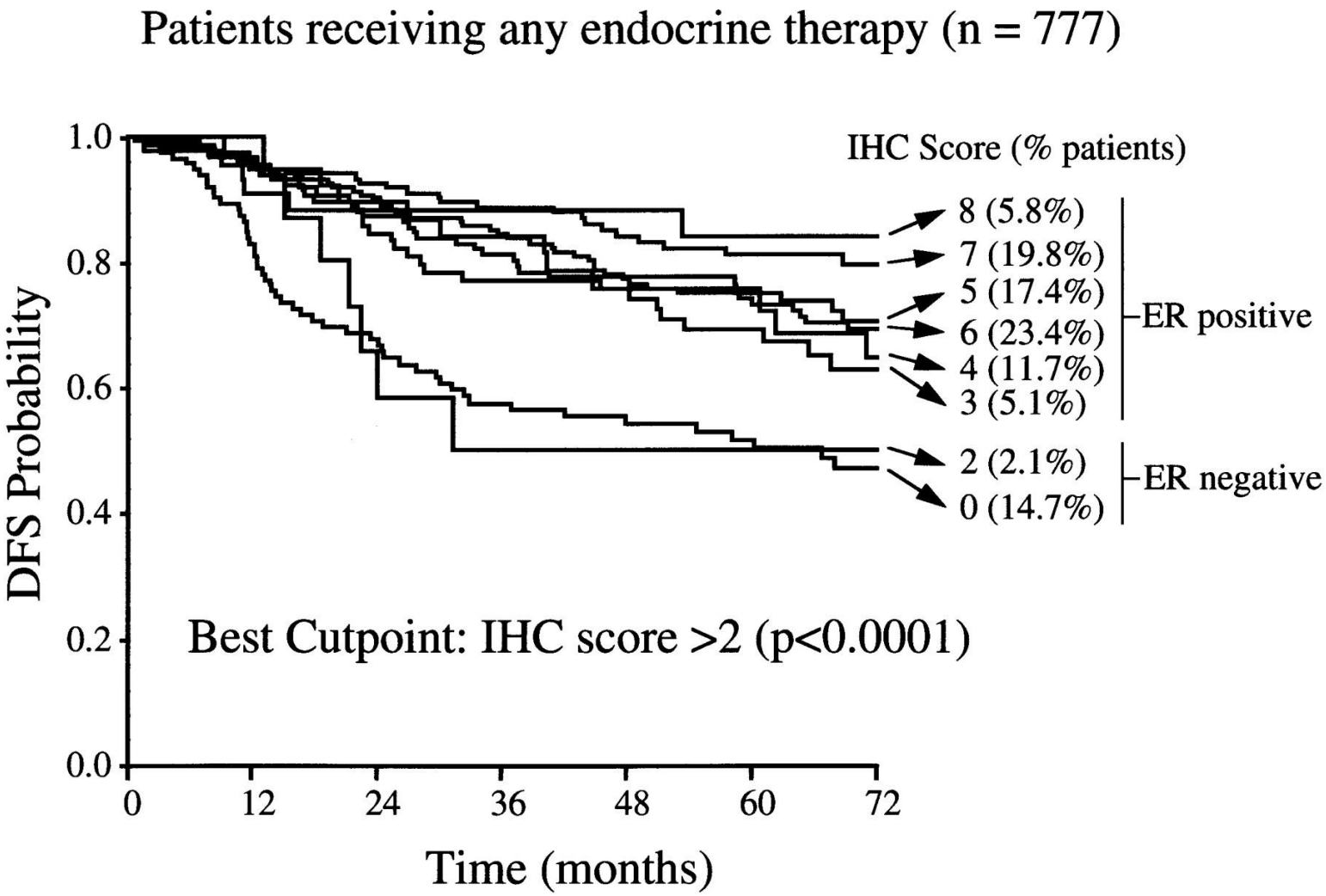
ER pos and ER neg BC are different diseases





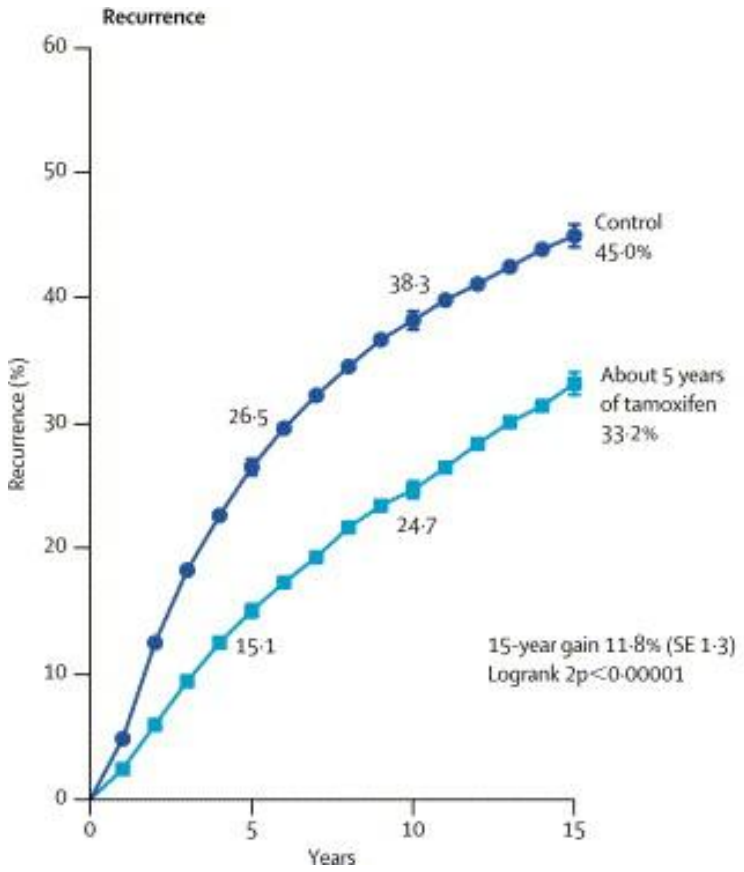
Sorlie T e al, PNAS 2001.

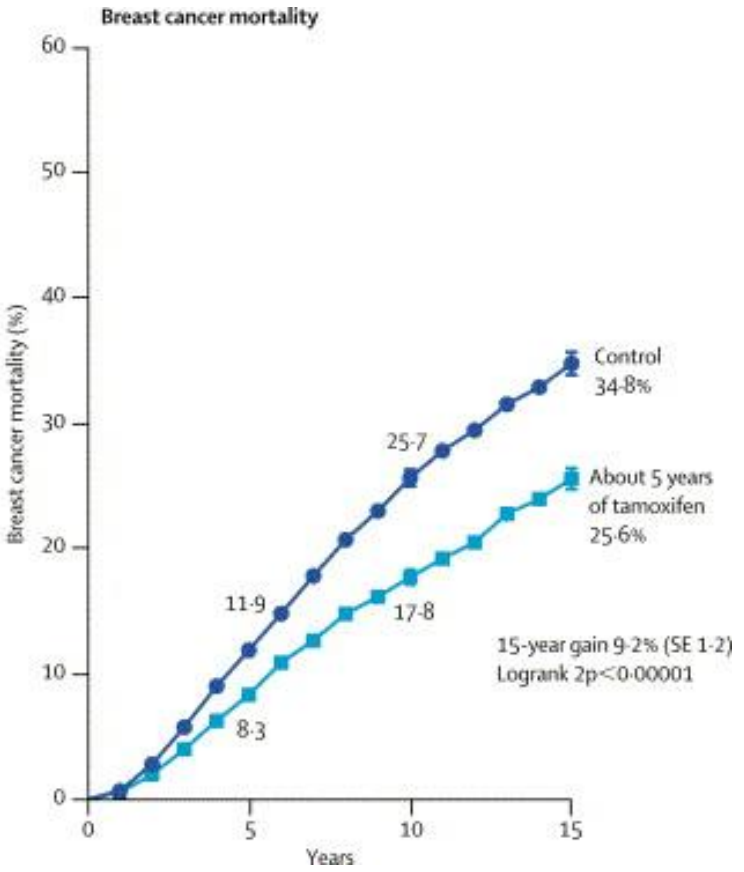
Response to anti-E2 treatment relates to ER expression



Harvey J M et al. JCO 1999;17:1474-1474

Focus on tamoxifen





Early Breast Cancer Trialists' Collaborative Group (EBCTC). Lancet, 2005

Adjuvant on line: benefit of tamoxifen

Age: 50 General Health: Excellent

Estrogen Receptor Status: Positive Histologic Grade: 2
Tumor Size: > 5.0 cm Nodes Involved: 1 - 3
Chemotherapy Regimen: Third Generation Regimen

Decision: No Additional Therapy

53 out of 100 women are alive in 10 years.
45 out of 100 women die because of cancer.
2 out of 100 women die of other causes.

Decision: Hormonal Therapy

12 out of 100 women are alive because of therapy.

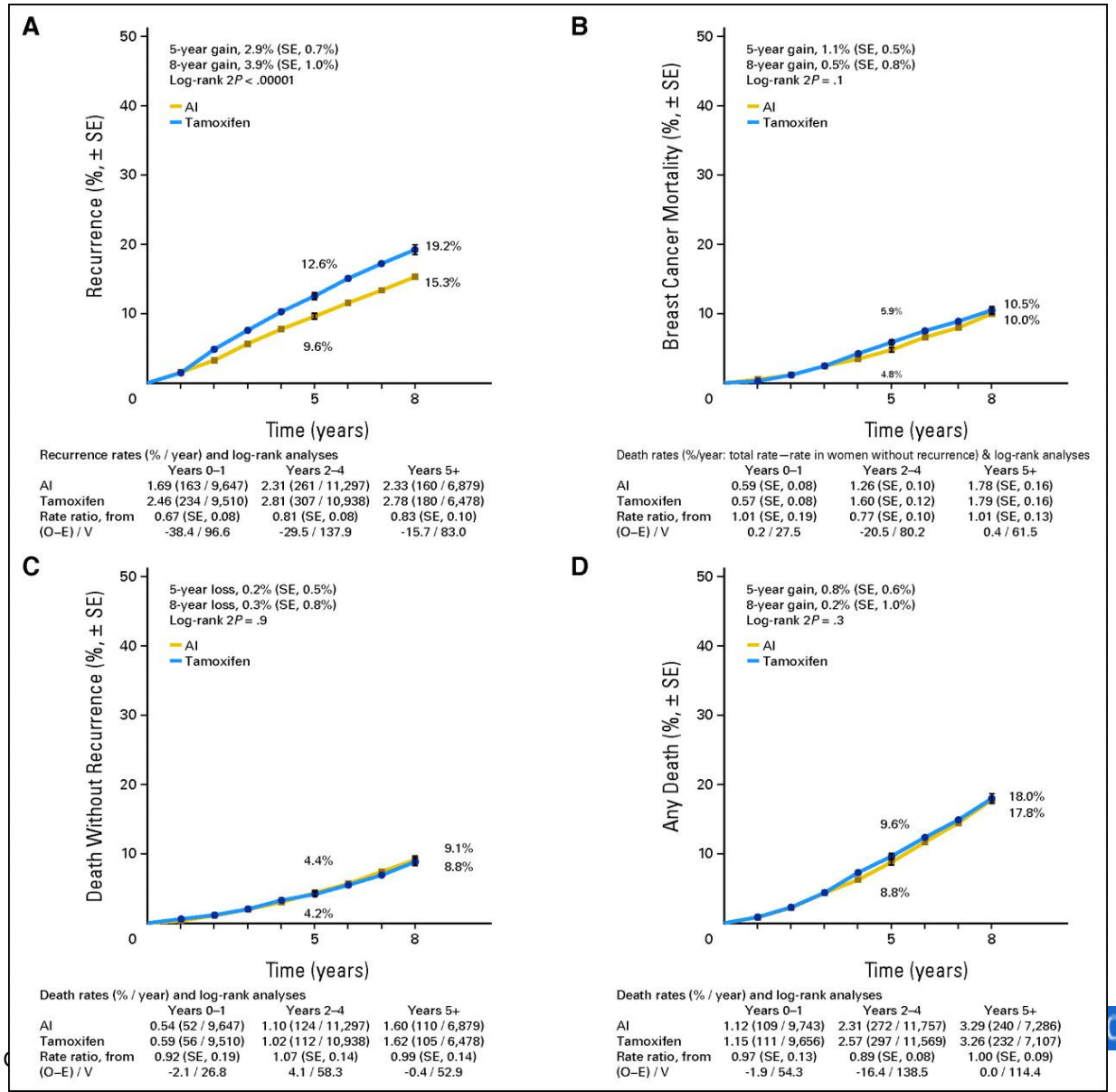
Decision: Chemotherapy

17 out of 100 women are alive because of therapy.

Decision: Combined Therapy

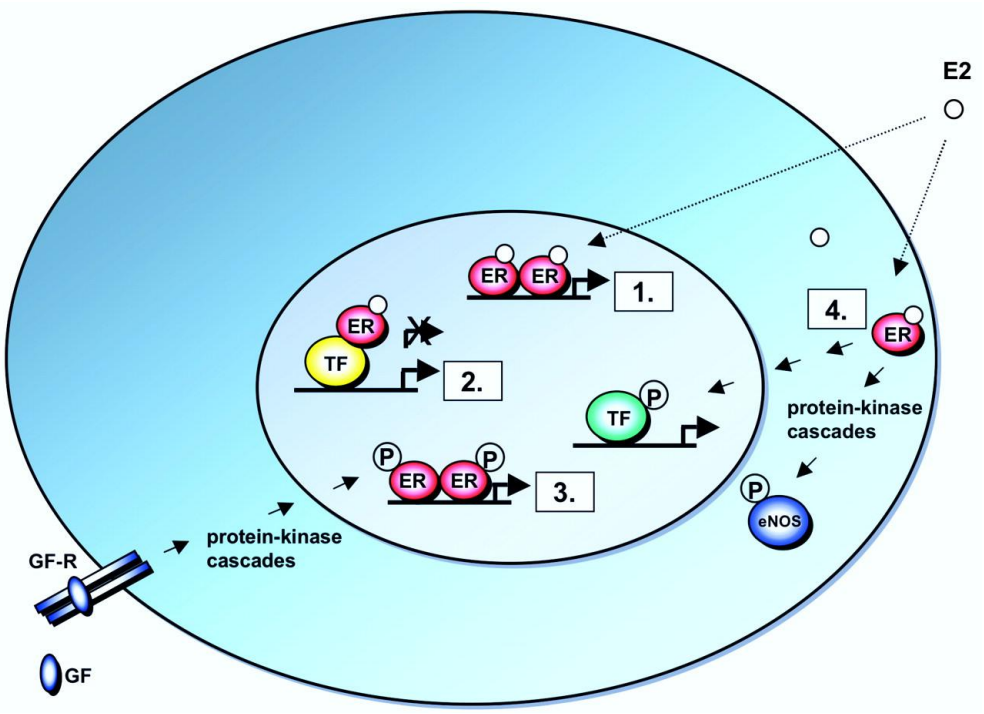
25 out of 100 women are alive because of therapy.

Life-table curves of (A) recurrence; (B) breast cancer mortality; (C) death without recurrence; and (D) any death, for estrogen receptor–positive patients in trials of approximately 5 years of aromatase inhibitor (AI) versus tamoxifen.



Over view of hormone manipulation of ER pos, metastatic breast cancer (men and post-men. women)

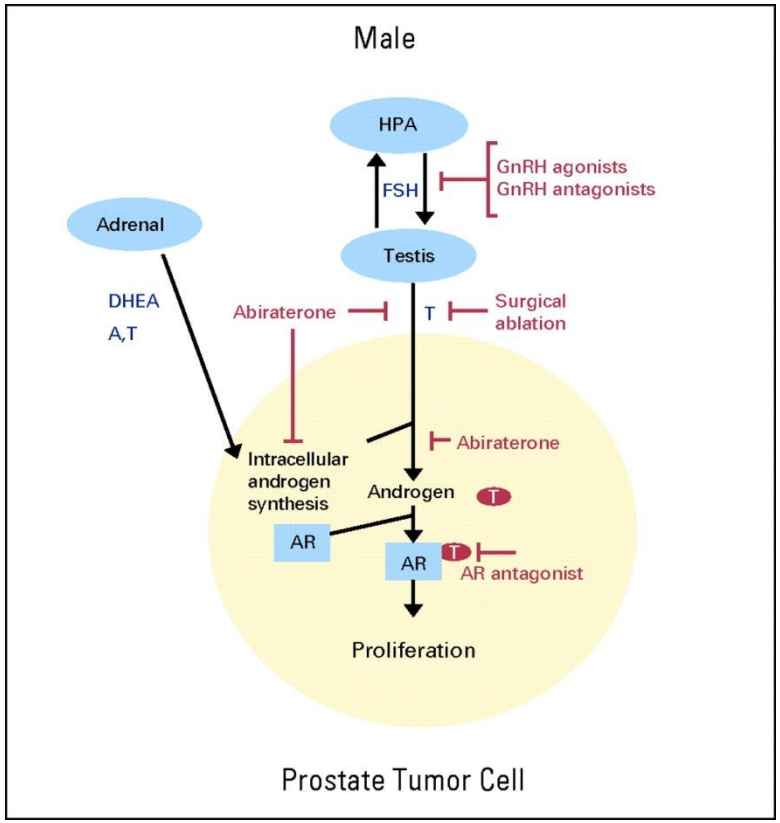
Overcoming endocrine resistance



mTOR inhibitors and AI

- PI3K –mTOR pathway dysregulated in estrogen resistant ER-pos cancer
- BOLERO-2: everolimus/ placebo+ exemestane
- Phase 3
- Median PFS: 10.6m vs 4.1

Prostate Cancer



Androgens from the adrenal glands account for 10–30% of serum androgens dehydroepiandrosterone (DHEA) and other precursor steroids secreted by the adrenal glands can be converted into potent androgens

Targeting androgen signalling in prostate cancer

- surgical castration
- chemical castration
- antiandrogens (flutamide and bicalutamide)
- adrenal androgen synthesis may be suppressed in castrate patients using the 17,20 lyase inhibitor, abiraterone acetate.

Focus on abiraterone

- (CYP)17CYP17 is a key enzyme with dual functions of 17α-hydroxylase and C17,20-lyase activity, necessary for both adrenal and intratumoral *de novo* biosynthesis of androgen hormones
- Abiraterone acetate is a small-molecule inhibitor of cytochrome P450 (CYP)17CYP17

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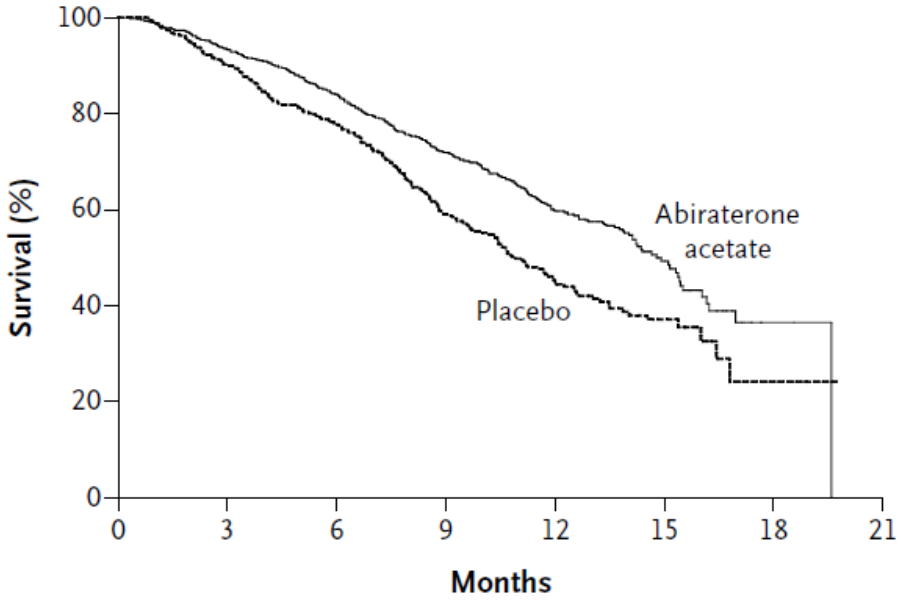
Abiraterone and Increased Survival in Metastatic Prostate Cancer

Johann S. de Bono, M.B., Ch.B., Ph.D., Christopher J. Logothetis, M.D., Arturo Molina, M.D., Karim Fizazi, M.D., Ph.D., Scott North, M.D., Luis Chu, M.D., Kim N. Chi, M.D., Robert J. Jones, M.D., Oscar B. Goodman, Jr., M.D., Ph.D., Fred Saad, M.D., John N. Staffurth, M.D., Paul Mainwaring, M.D., M.B., B.S., Stephen Harland, M.D., Thomas W. Flaig, M.D., Thomas E. Hutson, D.O., Pharm.D., Tina Cheng, M.D., Helen Patterson, M.D., John D. Hainsworth, M.D., Charles J. Ryan, M.D., Cora N. Sternberg, M.D., Susan L. Ellard, M.D., Aude Fléchon, M.D., Ph.D., Mansoor Saleh, M.D., Mark Scholz, M.D., Eleni Efstathiou, M.D., Ph.D., Andrea Zivi, M.D., Diletta Bianchini, M.D., Yohann Loriot, M.D., Nicole Chieffo, M.B.A., Thian Kheoh, Ph.D., Christopher M. Haqq, M.D., Ph.D., and Howard I. Scher, M.D., for the COU-AA-301 Investigators*

A Overall Survival



No. at Risk								
Abiraterone acetate	797	736	657	520	282	68	2	0
Placebo	398	355	306	210	105	30	3	0

Toxicity of anti-cancer hormonal manipulations

- Tamoxifen
  - Weight gain
  - Menopausal symptoms
  - Endometrial ca
  - DVTs
- AI
  - Osteoprosis
  - Joint discomfort
  - Menopausal symptoms
- Anti-androgens
  - Osteoporosis
  - Impotence

Questions.....